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# Process-based versus product-based assessments of genetically modified plants, animals and micro-organisms

BO project 43-112-001

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[REDACTED], [REDACTED], [REDACTED], [REDACTED]

\* Hereby we would like to acknowledge the contribution of [REDACTED], who contributed significantly to the draft of this report. Due to the termination of her employment at WFSR, she was not involved in the completion of the report and had no voice in its final content. Since she cannot be held accountable for the final content, she is not listed among the authors above

This research has been carried out by Wageningen Food Safety Research, institute within the legal entity Wageningen Research Foundation subsidised by the Dutch Ministry of Agriculture, Nature and Food Quality (project BO-43-112-001).

Wageningen, April 2021

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WFSR report 2021.506

5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e 2021. *Process-based versus product-based assessments of genetically modified plants, animals and micro-organisms; BO project 43-112-001*. Wageningen, Wageningen Food Safety Research, Confidential WFSR report 2021.506. 128 pp.; 0 fig.; 7 tab.; 72 ref.

Project number: 1287364901

BAS-code: BO-43-112-00

Project title: Ontwikkeling methodiek voor product-gebaseerde borging voedselveiligheid

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# Executive summary

Genetically modified organisms (GMOs) may only enter the (European) market after a pre-market assessment of their safety for food and feed use and for the environment. The European Union regulations in this field are enforced by member state authorities by means of DNA-based methods that can be used to identify all approved GMOs. These methods also have the potential to detect and identify at least part of the unauthorised GMOs that may be present in raw materials and related food or feed products.

In recent years, gene-editing techniques to modify the genetic code have been introduced, of which CRISPR-Cas9 is the best known. These techniques operate more precisely than traditionally used methods, because they allow changes at predefined region in the genome. Gene-editing techniques feature prominently amongst the so-called new breeding techniques (NBTs). They currently fall under the regulations for GMOs, as clarified by the decision of the Court of Justice of the European Union in 2018. As these NBTs have many applications and are relatively simple to use, it is likely that food or feed products that are derived from these may enter the European market in the near future. However, these cannot be as easily identified as first generation GMOs, as the modifications introduced with gene editing can often not be distinguished from natural mutations.

In this project, the developments with NBTs are analysed for three sectors: plant, animal, and microbiology. Based on literature research and a series of interviews with experts, stock was taken of the envisaged consequences of the application of NBTs, including traceability, safety, economics, regulatory aspects and societal aspects. The possible transition from (current) process-based to (more) product-based regulations received special attention.

## **Developments**

Our analysis of developments in the plant breeding sector shows that new varieties are created using NBTs, often by means of CRISPR-Cas based methods. The application of NBTs enables faster development of new breeds in plant breeding, although the resulting new varieties themselves are not necessarily created with gene editing. This is because faster breeding of new varieties with plants is possible by using traditional breeding practices and traditional mutagenesis techniques (that are exempted from GMO legislation) guided by the selection of genes whose functions have been established with experimental gene editing. However, experts believe that varieties that have been edited themselves will reach the European market shortly (within 3 years).

In the microbiology sector gene-editing emerges as the most important innovation. Gene edited micro-organisms are already used: in the USA, for example, products are already being marketed that contain gene-edited organisms, such as beer yeasts. Some experts believe that products derived from gene-edited micro-organisms are already on the EU market such as enzymes and amino acids. Since these do not contain the organism or its DNA, these products are exempt from the requirement for regulatory approval as a GM food or feed.

In the animal sector, gene editing is mainly still in the research stage, for various species and traits. The interviewed experts do not consider NBTs as most important development in this sector. Moreover, experts expect that there will be no products from gene-edited animals entering the (European) market within the next five years.

## **Traceability**

Event-specific methods are available for GMO events that are authorised in the EU. It is possible to make methods for particular DNA sequences – even the smallest, single nucleotide variations, yet the origin of such variations cannot be unequivocally be established. Therefore, it is not possible to prove illicit marketing of unauthorised, NBT-derived products based on DNA methods or sequences.

Traceability of gene-edited organisms is seen as problematic in all three sectors. In plant breeding,

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there will be particular challenges for international companies that work with plants from areas with different regulations, so that gene editing-free status cannot be guaranteed. In livestock breeding, (re)establishment of traits in various breeds that are known in/from other breeds will likely be used most, whereby origin (conventionally bred or introduced with NBTs) cannot be distinguished. It may be possible to use whole genome sequencing to detect and/or identify transgenic sequences, gene insertions or gene deletions in gene -edited organisms. However, this is only when valid reference information is available, in the form of a reference genome. The WGS-approach will be futile to track down small genomic modifications in unauthorized microbial strains, plants or animals lacking background information, as the genetic changes will be undistinguishable from those that occur naturally.

It is technically feasible to trace specific traits in the genome, which would enable a product-based legislation. However, a product-based approach will have downsides as well, mainly in the sheer number of products. It will be impossible to identify every new product, therefore any enforcement should be risk based.

### **Safety**

In the short term, there are few safety risks expected with NBTs because market parties are expected to ensure safety of new varieties and products. Particularly in plant breeding and microbiology, NBTs may enhance the safety of new organisms, as the new techniques are more precise than the common, traditional mutation breeding techniques.

Off-target effects in plants and industrial microbiology are generally not a main concern, where mutation breeding is common practice. Guidelines on assessing (and preventing) off-target effects in the early stages of plant breeding (and industrial microbiology) may further optimise safety. Certain types of developments may pose more risks for safety, such as the introduction of new metabolic routes (in plants and micro-organisms, and possibly in animals in a more distant future) which requires extra careful consideration. In certain plants, anti-nutrients and natural toxins are present that require attention, particular in combination with quicker, NBT-enabled domestication. In addition, modifications aimed at resistance, particularly relevant in plants, could be more relevant to human health.

Moreover, the combination of an increased number of modified organisms with shorter development time, may give rise to safety risks so far not foreseen. Monitoring of global developments enables timely identification of worrisome developments and of developments that need further scrutiny. Within the animal sector, animal health and welfare are main concerns for animal breeders that are considering to use gene editing technologies. Off-target effects can have far fetching consequences for animals, mainly for their safety and well-being, and should therefore be a major point of attention if NBTs are applied in animals. Safety assessments that are scientific and risk-based are advocated by the experts, with an early recognition of potential safety issues. The integration of safety considerations in all stages of research and development and production, also known as Safe-by-Design, is advocated. The Safe-by-Design concept is well-known in microbiology, and in line with the way of working in companies. Within this project, we also advocate for the application of Safe-by-Design for crop breeding innovations.

The Safe-by-Design approach does not have any applications in the animal sector so far, but because the concept appeals to experts, it may be promising to promote the approach here as well.

### **Societal aspects**

The opposition against GMOs from non-governmental organisations and consumers, is also there for gene-edited products. Overall, the acceptance of GMOs and NBTs for food-related purposes is highly variable amongst consumers. This opposition can arise from multiple considerations and combinations thereof, including safety concerns regarding novel techniques, fundamental objections against the use of these technologies for food and feed, concerns about the distribution of benefits and negative consequences over various stakeholders, and wider concerns regarding the agricultural sector. Overall, the use of GM techniques in the animal sector is most controversial, followed by the use in plants. There is relatively little opposition against the use of GM and gene editing techniques in the

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industrial microbiology sector, which may be caused by a lack of awareness or a lack of affinity with the subject.

Experts from different sectors express their concern about the polarisation in discussions on GM and NBTs, and characterized them as unbalanced with mixing of technical risks and more fundamental concerns. Labelling gives an opportunity for consumers to choose GM and gene-editing free products.

### **Regulatory aspects**

The current GMO-related legislation in the EU is process-based, although the safety assessment has a product-based character for previously assessed expressed products based on their familiarity. If a product-based legislation were to be applied, the particular assessment of products would need to be decided for on a case-by-case basis. Particular products with a significant risk for food safety, according to EU standards, would then need to undergo an assessment.

With regards to regulatory aspects, it is noted that nations worldwide are facing similar challenges with the consequences of NBTs, which calls for international harmonisation. Linking the regulatory safety assessment with international principles and guidelines may be feasible. Harmonisation with other states or regulatory aggregates may be feasible, for which the experts name Australia, New Zealand, Japan, and USA as examples. In the animal breeding sector, experts plead for more opportunities to do research with NBTs to obtain more experience.

There are heavy regulatory burdens in Europe, which give particularly small companies a disadvantage versus large companies. Separation between requirements for safety assessment and those for labelling may be an opportunity.

In a series of three workshops, different legislative scenarios were discussed with Dutch scientists from academia and business. The scenario's included the current, mainly process-based situation, a product based legislation, and three alternative scenarios: small gene edits exempted from regulation (SDN-1 and SDN-2), a new GMO definition in which SDN-1-derived organisms are no longer considered GMOs and altered risk assessment for gene-edited organisms (decreased data requirements compared to traditional GMO's).

In the plant breeding workshop, the scenario where small modifications are exempted from GMO regulation was most popular. It enables the use of techniques, may actually increase food safety (owing to higher precision of gene edited compared to random mutagenesis and cross breeding), and resolves issues regarding traceability, as only plants containing introduced foreign DNA need to be traced. It is considered a quick fix, and more future-proof legislation is still desirable. Product-based legislation is not considered a good alternative, as lengthy procedures may be required for crops that are currently exempted, while there is no argument that food safety is actually impaired.

In contrast, in the microbiology workshop a product-based approach is most popular, as the case-by-case approach enables to be tailored to new or modified products, in line with potential hazards posed by the novel product. The current process-based situation is considered to be least favorable, gene editing is considered safer than random mutagenesis methods, and the long approval procedures in Europe hinder innovation.

Particularly in the workshop with the livestock breeding sector, participants found it difficult to judge the suitability of the scenarios. Animal wellbeing should be guaranteed, regardless of the legislative scenario. Moreover, an inclusive way in forming new legislation with public involvement was advocated.

### **Conclusion**

Gene editing is an emerging technology, particularly in the fields of microbiology and plant breeding. There is a clear distinction between the three different sectors (plant, animal, and microbiology) in their preferences for the type of regulation. The regular use of mutagenesis breeding (plant, microbiology) and contained use (microbiology) are important causes of this distinction.

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The current European process-based regulation for GMOs is considered a threat in the long run by stakeholders from all three sectors, as there is little opportunity for innovation using novel techniques. A transition to a more product-based regulation may reduce this, however only in case risk assessment and judgement are scientifically sound and in proportion to risks. Assessment and enforcement of (new) products should be risk-based, otherwise they will be too burdensome for both industry and enforcing authorities.

Furthermore, the distinction between process-based and product-based regulations is not definite, process-based regulations can include product-based principles and vice-versa.

Regardless of the regulatory framework being process-based or product-based, working according to the Safe-by-Design principles when applying NBTs, is a promising strategy. Applying Safe-by-Design will aid in the completion of a safety dossier for market approval and will contribute to the development of safe products.

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# Nederlandstalige Samenvatting

Genetisch gemodificeerde organismen (GGOs) mogen in Europa alleen in de handel gebracht worden na toetsing op voedsel-, diervoeder- en milieuveiligheid. De regelgeving van de Europese Unie wordt gehandhaafd door de bevoegde autoriteiten van de lidstaten, met DNA-gebaseerde methodes die alle toegestane GGOs kunnen aantonen. Naast het gebruik voor detectie van toegestane GGOs, kunnen deze methoden ook gebruikt worden om ten minste een deel van de ongeautoriseerde GGOs te detecteren en identificeren, zowel in onbewerkte als bewerkte voedselproducten.

In de afgelopen jaren zijn de zogenaamde 'gene editing' technieken ontwikkeld, waarvan CRISPR-Cas9 de bekendste is. Deze technieken opereren nauwkeuriger dan de traditioneel gebruikte methoden, en op vooraf gedefinieerde plaatsen in het genoom. Gene editing technieken zijn de belangrijkste categorie van de zogenaamde nieuwe veredelings technieken (NVTs; in het engels bekend als new breeding techniques (NBTs)). Deze vallen momenteel onder de GMO regelgeving in de EU, zoals bevestigd door de beslissing van het Europese hof van Justitie in 2018. Omdat deze NVTs talrijke (veelbelovende) toepassingen hebben en relatief makkelijk in gebruik zijn, is het waarschijnlijk dat voedselproducten en veevoeders afkomstig van deze technieken binnenkort in de handel gebracht zullen worden in Europa. Echter, deze producten zullen niet zo makkelijk geïdentificeerd kunnen worden als conventionele, eerste generatie GGOs, omdat modificaties geïntroduceerd met gene editing vaak niet te onderscheiden zijn van natuurlijke mutaties.

In dit project worden de ontwikkelingen van NVTs geanalyseerd voor drie sectoren: plant (veredeling), dier (met name veehouderij) en (industriële) microbiologie. Aan de hand van literatuuronderzoek en een serie interviews met experts worden de consequenties van de toepassingen van NVTs geanalyseerd, waarbij voornamelijk naar traceerbaarheid, veiligheid, regelgeving, en economische en maatschappelijke aspecten is gekeken. De mogelijke overgang van de huidige proces gebaseerde regelgeving naar alternatieven, zoals een (meer) product gebaseerde regelgeving, heeft extra aandacht gekregen.

## Ontwikkelingen

Onze analyse van de ontwikkelingen met NVTs, laat zien dat er binnen de plantveredeling nieuwe variëteiten worden gecreëerd met deze nieuwe technieken, vaak door middel van de toepassing van CRISPR-Cas gebaseerde methoden. De toepassing van NVTs maakt snellere ontwikkeling van nieuwe variëteiten mogelijk, hoewel de nieuwe variëteiten niet noodzakelijkerwijs direct met NVTs hoeven te zijn gemaakt. Door de kennis van genen en hun functies, verkregen met NVTs, in te zetten zijn snellere veredeling en selectie met conventionele veredelings technieken en mutagenese technieken mogelijk (die uitgezonderd zijn van GGO regelgeving) Echter, experts verwachten dat ook variëteiten die wel direct met NVTs zijn ontwikkeld waarschijnlijk op korte termijn (binnen 3 jaar) hun opmars zullen maken op de Europese markt.

In de microbiologie wordt gene-editing als de belangrijkste ontwikkeling gezien. Micro-organismen met gene edits worden al gebruikt, bijvoorbeeld in de VS worden producten verhandeld die gene-edited organismen bevatten, bijvoorbeeld bier met biergist. Sommige experts denken dat producten afkomstig van gene-edited micro-organismen al in de EU op de markt zijn, zoals enzymen en aminozuren. Aangezien producten waar geen (DNA van) gemodificeerde organismen meer aanwezig is, zijn uitgezonderd van de regelgeving, hoeven zij niet eerst goedgekeurd te worden voordat ze in Europa verhandeld mogen worden.

Het gebruik van gene editing in dieren bevindt zich nog in de onderzoeksfase, waarbij verscheidene soorten en eigenschappen worden onderzocht. De geïnterviewde experts beschouwen de toepassing van NVTs momenteel niet als meest belangrijke ontwikkeling in de sector. Daarnaast is de verwachting dat er de komende vijf jaar geen producten afkomstig van gene-edited dieren in de handel gebracht zullen worden in Europa.



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## Traceerbaarheid

Er zijn methodes specifiek voor de transformatiestap ('stapspecifiek' oftewel event-specifiek) beschikbaar voor alle GGO's die in de EU zijn toegestaan. Daarnaast is het mogelijk om methodes te maken voor DNA sequenties, zelfs voor de kleinste variaties van een nucleotide, maar de oorsprong van zulke variaties kan niet met zekerheid worden vastgesteld. Daarom is het niet mogelijk om frauduleuze verhandeling van niet-geautoriseerde, van NVTs afkomstige producten op basis van DNA-methodes of sequenties te bewijzen.

De traceerbaarheid van gene-edited organismen wordt in alle drie de onderzochte sectoren als problematisch beschouwd. Daarnaast zijn er in de plantenveredeling uitdagingen voor internationaal opererende bedrijven die werken met planten uit verschillende regio's wereldwijd, waar regelgeving kan verschillen en een gene-editing vrije status niet altijd gegarandeerd kan worden. In de veehouderij zijn er met name kansen voor het (her)introduceren van eigenschappen die bekend zijn uit verwante rassen, waarbij de oorsprong (conventioneel gefokt of geïntroduceerd met NVTs) niet kan worden onderscheiden. 'Whole genome sequencing' (WGS) (het in kaart brengen van hele genomen) kan gebruikt worden om transgene sequenties, inserties en deleties op te sporen in gene-edited organismen, maar alleen indien er een valide referentiegenoom beschikbaar is. Echter, WGS kan niet gebruikt worden voor het opsporen van door NVTs geïntroduceerde kleine modificaties in ongeautoriseerde GG-microbiële stammen, planten of dieren als er geen achtergrondinformatie (referentiegenoom) aanwezig is, omdat dit type genetische veranderingen niet te onderscheiden is van natuurlijk optredende veranderingen.

Het is technisch mogelijk om bepaalde eigenschappen te traceren door naar het genoom te kijken, waardoor een product-gebaseerde regelgeving mogelijk is. Hierbij zijn echter ook nadelen, met name in de hoeveelheid van (nieuwe) producten die in de handel zijn of worden gebracht. Het is niet mogelijk om ieder nieuw product te identificeren, dus in de praktijk zal er gekozen moeten worden voor handhaving die met name kijkt naar producten met een hoog risico.

## Veiligheid

Op korte termijn worden er weinig veiligheidsrisico's verwacht als gevolg van het gebruik van NVTs. Marktpartijen zullen de veiligheid van nieuwe variëteiten en nieuwe producten garanderen. In de plantenveredeling en industriële microbiologie kan het gebruik van NVTs de veiligheidsrisico's zelfs nog verder verkleinen, omdat de nieuwe technieken veel preciezer opereren dan de huidige, veelgebruikte mutatieverdelingstechnieken.

Modificaties op andere dan de bedoelde locatie in het genoom ('off-target' modificaties), zijn geen reden voor bezorgdheid in de plantenverdeling en de industriële microbiologie, waar mutatieveredeling gebruikelijk is voor het creëren van nieuwe variëteiten en microbiële stammen. Richtlijnen voor het beoordelen (en voorkomen) van off-target effecten in de vroege stadia van ontwikkeling kunnen bijdragen aan het verder optimaliseren van (voedsel)veiligheid. Desalniettemin zijn er ook ontwikkelingen die meer risico's voor (voedsel)veiligheid met zich meebrengen, zoals de introductie van nieuwe metabole routes (in planten en micro-organismen, en op termijn mogelijk ook in dieren). Ook planten die van nature toxines en anti-nutriënten bevatten vragen om specifieke aandacht, zeker wanneer er sprake is van versnelde domesticatie door middel van NVTs. Modificaties die gericht zijn op resistentie, bijvoorbeeld tegen plaaginsecten of herbiciden, kunnen mogelijk meer relevantie hebben voor humane gezondheid.

De combinatie van een toegenomen aantal van gemodificeerde organismen met een kortere ontwikkeltijd, zou tot veiligheidsrisico's kunnen leiden die momenteel nog niet zijn voorzien. Het monitoren van de ontwikkelingen wereldwijd maakt het mogelijk om tijdig zorgelijke ontwikkelingen en ontwikkelingen die nader onderzoek nodig hebben, te identificeren.

De diersector verschilt van de plant en microbiologie sectoren, omdat de veiligheid van een product niet het belangrijkste aandachtspunt is, maar juist de gezondheid en het welzijn van het dier. Daarnaast kunnen off-target effecten drastische gevolgen hebben voor dieren, met name voor hun veiligheid en welzijn, en daarom moeten off-target effecten een belangrijk punt van aandacht zijn als NVTs gebruikt gaan worden in dieren.

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De experts pleiten voor veiligheidsbeoordelingen die wetenschappelijk en risico-gebaseerd zijn, waarbij al vroeg nagedacht wordt over mogelijke veiligheidsrisico's. De integratie van veiligheidsoverwegingen in alle fases van R&D en productie, beter bekend als 'Safe-by-Design', wordt aanbevolen.

Het Safe-by-Design principe is goed bekend in de microbiologie, en is in lijn met de manier waarop bedrijven werken. In dit project promoten we het gebruik van Safe-by-Design voor de plantenveredeling. Het Safe-by-Design principe heeft nog geen toepassingen bij dieren, maar het concept spreekt de experts aan; er liggen kansen om het gebruik van Safe-by-Design te promoten en gebruiken.

De maatschappelijke weerstand van non-profit organisaties en consumenten en tegen GGO's is er ook voor gene-edited producten. De acceptatie van genetische modificatie en NVTs voor voedsel gerelateerde doelen verschilt sterk onder de consumenten. Deze weerstand kan vele en verschillende oorzaken hebben, waaronder zorgen over de veiligheid van nieuwe technieken, maar ook meer principiële bezwaren, en zorgen over de verdeling van de positieve en negatieve consequenties van de technieken zelf, of zorgen over de landbouw in het algemeen.

Het gebruik van genetische modificatie technieken is het meest controversieel bij dieren, gevolgd door het gebruik in planten. Er is relatief weinig bezwaar tegen het gebruik van GGO's en gene-edited organismen in de industriële microbiologie; mogelijk omdat dit minder bekend is bij het publiek of omdat men er minder affiniteit mee heeft.

Experts van de verschillende sectoren uitten hun bezorgdheid over de polarisatie in de discussies over genetische modificatie en NVTs, en karakteriseren de discussies als ongebalanceerd, waarbij technische risico's en principiële bezwaren op een onjuiste manier gemixt worden. Etikettering geeft consumenten de optie om voor GGO en gene-edited vrije producten te kiezen.

### **Regelgeving**

De huidige GGO regelgeving in de EU is proces gebaseerd, ook al heeft de veiligheidsbeoordeling een product gebaseerd karakter voor producten die al bekend en eerder goedgekeurd zijn. Als een product gebaseerde regelgeving toegepast zou worden, dient op een case-by-case basis besloten te worden of en in hoeverre nieuwe producten beoordeeld moeten worden. Producten met een hoger risico voor de voedselveiligheid zouden een veiligheidsbeoordeling moeten ondergaan.

De experts merken op dat wanneer het op regelgeving aankomt, de dilemma's wereldwijd vergelijkbaar zijn, wat internationale harmonisatie mogelijk zou kunnen maken. Het combineren van veiligheid met internationale principes en voorschriften kan een mogelijkheid zijn. Harmonisatie met andere landen of unies is ook mogelijk, met name Australië, Nieuw-Zeeland, Japan en de Verenigde Staten als voorbeelden. In de dierensector pleiten de experts voor meer mogelijkheden om onderzoek te doen met NVTs, om zo ervaring op te doen.

De regelgeving omtrent GGO's is een aanzienlijke last voor bedrijven, en dat is met name voor kleine(re) bedrijven nadelig. Een onderscheid maken tussen de regelgeving voor veiligheidsbeoordeling en voor etikettering kan een kans zijn.

In een serie workshops zijn verschillende scenario's voor regelgeving besproken met wetenschappers en experts uit het bedrijfsleven. De scenario's omvatten de huidige proces gebaseerde regelgeving, een product gebaseerde regelgeving, en drie alternatieve scenario's: uitzondering van regelgeving voor kleine edits (i.e. SDN-1 en SDN-2), een nieuwe GMO definitie (SDN-1 niet als GGO beschouwen), en een alternatieve veiligheidsbeoordeling voor gene-edited organismen (minder data in vergelijking met traditionele GGO's).

In de workshop over plantenveredeling, was het scenario waarbij kleine modificaties worden uitgezonderd van regelgeving het meest populair. De belangrijkste redenen waren: 1) dit scenario maakt het gebruik van NVTs mogelijk, 2) door grotere precisie van de NVTs (tov conventionele mutagenese en kruisingen) kunnen de voedselveiligheidsrisico's verder verminderd worden en 3) de

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problemen rondom traceerbaarheid van gene-edited producten kunnen worden opgelost, aangezien alleen planten met transgeen DNA getraceerd hoeven te worden. Er werd wel opgemerkt dat dit scenario een 'snelle oplossing' is, en dat regelgeving nog verder toekomstbestendig gemaakt moet worden.

In de workshop over microbiologie was juist de product gebaseerde benadering het meest populair, omdat de case-by-case aanpak van dit scenario het mogelijk maakt de veiligheidsbeoordeling aan te passen op basis van het product, in overeenstemming met de veiligheidsrisico's die het nieuwe product met zich meebrengt. De huidige proces gebaseerde situatie wordt het minst gewaardeerd, omdat gene editing als veiliger wordt beschouwd dan random mutagenese, en dat de lange toelatingsprocedures in de EU innovatie hinderen.

Met name in de workshop over dieren vonden de deelnemers het moeilijk om de geschiktheid van de scenario's te beoordelen. Het welzijn van dieren moet gegarandeerd worden, onafhankelijk van de regelgeving die geldt. Daarnaast werd gepleit voor het betrekken van het publiek bij het maken van nieuwe regelgeving.

### **Conclusie**

Gene editing is een opkomende technologie, met name in de microbiologie en in de plantenveredeling. In de drie hier onderzochte sectoren (plant, dier en microbiologie) is er verschil in voorkeur voor de grondslag van de regelgeving voor GGOs. De huidige toepassing van mutagenese technieken in veredeling (plant, microbiologie) en de mogelijkheid tot ingeperkt gebruik (microbiologie) zijn belangrijke oorzaken van dit onderscheid.

De huidige, proces gebaseerde regelgeving voor GGOs wordt door stakeholders uit alle drie de sectoren gezien als een bedreiging op lange termijn, omdat er weinig mogelijkheden zijn voor innovaties met de NVTs. Een overgang naar een product gebaseerde regelgeving kan die dreiging verminderen, maar alleen als de risicobeoordeling wetenschappelijk gebaseerd is en in verhouding tot de risico's staat. Beoordeling en handhaving van (nieuwe) producten moet risico gebaseerd zijn, omdat deze anders een te zware last leggen op de industrie en de handhavende autoriteiten.

Het onderscheid tussen proces gebaseerde en product gebaseerde regelgeving is niet absoluut: in een proces gebaseerde regelgeving kunnen product gebaseerde elementen zijn opgenomen, en vice-versa.

Onafhankelijk van basis van de regelgeving, het werken volgens Safe-by-Design principes wanneer NVTs worden toegepast, is een veelbelovende strategie. Safe-by-Design helpt bij de dossiervorming voor markttoelating en draagt bij aan de ontwikkeling van veilige producten.

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# 1 General introduction

Genetically modified organisms (GMOs) may only enter the (European) market after regulatory approval, prior to which they have to undergo a pre-market assessment of their safety for food and feed use and for the environment. The European regulations in this field are enforced amongst others by inspection agencies verifying the presence of GMO-derived products in food and feed. For this, they have at their disposal DNA-based methods that can identify all approved GMOs, as well as some others with the potential to detect and identify at least part of the unauthorised GMOs that may be present in raw materials and related food or feed products.

New breeding techniques (NBTs), such as CRISPR-Cas, have been identified in 2018 by the European Court of Justice as techniques that will result in GMOs. It is likely that NBT-derived food or feed products may enter the European market via imports in the near future due to the application of NBTs in exporting countries. These cannot easily be identified as GMOs however, as the resulting modifications often cannot be distinguished from natural mutations and. Furthermore it will not be possible to identify the technique(s) applied.

This project will analyse the consequences of these developments, with a focus especially on the possible transition from process-based to (more) product-based regulations, on the basis of literature reviews, in combination with expert views and the outcome of discussions with stakeholders.

To this end, three sectors have been assessed, for the specific aspects that are of relevance (developments, traceability, safety, economics, regulatory aspects, societal aspects), namely the plant, animal and microbiology sectors. The assessment is based on a literature review, combined with a series of interviews with experts in the respective fields, both from academia and from business, as well as a number of social scientists. The questionnaires from the interviews can be found in Annex 1, an overview of the interviewees in Annex 2, and the reports of the interviews in Annex 3. When the views of the experts in the interviews are described, this is always indicated in the heading above.

Finally, a series of workshops per sector with experts in the respective fields, both from academia and from industries, as well as a number of social scientists, to discuss the different legislative scenario's and their consequences.

## 1.1 Developments

Important developments in modern biology and biotechnology are ongoing. The toolbox for genetic alterations of genomes of micro-organisms, plants and animals has been extended with techniques to modify the genetic code at will, with increasing precision. The first techniques to modify the genomes were random, with no a priori determination where new genetic constructs were inserted into the genome, but this process has become more and more controlled, initially only in micro-organisms, but more recently also for plants and animals. Also, the extent of the direct modification has changed and is changing still. In micro-organisms, it has already proven feasible for many years to introduce new traits, and thus new expression products, without affecting the cell's organisation as such. In plants, the directed modification tools are more recent and have thus far mainly resulted in small insertions or deletions, or SNPs (single nucleotide polymorphisms), but this is now rapidly changing. With the increasing success rates of homology-directed recombination, it becomes within reach to make more profound changes in the plant's metabolism, in a directed way, thus reducing potential off-target effects.

In micro-organisms, the use of orthogonal microbial production systems is already routine. For plants this has so far been considered far off, but recent publications seem to indicate that also orthogonal plant, or even animal, production systems may not be far away anymore, to produce specific

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compounds (proteins, secondary metabolites) or composite products in a eukaryotic system. Also, this may increasingly not entail the modification of the genetic code as such, the DNA, but rather be effectuated by modifying the RNA, or by providing DNA fragments as a basis for (local) modification of the plant's/animal's physiology. It may also lead to changes at a larger scale, such as the accelerated domestication of plants that have not been applied for agricultural purposes so far, and therefore do not have a history of safe use. In recent years, additional species are increasingly considered for use in food and feed production, but also for environmental applications, such as algae, insects and worms. In the animal sector the focus may be on the production of specific (pharmaceutical) compounds that may benefit the husbandry animals directly, or may be harvested for commercial application, for men or animals. The reduction of animal disease prevalence may benefit the welfare of the animal simultaneously. Other applications that serve agronomic aims are being developed as well, such as the AquAdvantage salmon, that reaches its market size significantly faster compared to its conventional counterparts. This GM fish (GM animal) is now marketed in North America. Other species and related traits may follow, increasing the yield of muscles or milk or provide other economic advantages, or improve the organoleptic qualities of the product for the consumer.

## 1.2 Traceability

In a process-based regulatory strategy, it seems more important that a distinction can be made between authorised and non-authorised GMO-derived products, which may include products that have been gene-edited. The main reason for this, besides general enforcement of the legislation, is the consumer's choice for purchasing non-GMO products. In a product-based strategy, enforcement will clearly also be an issue, but here it will be more likely that, comparable to the current situation with novel foods, it may not be immediately clear in the market which products have evaded registration and therefore have not been assessed for their safety (yet). It seems plausible that the emphasis in practice will be more on safety aspects rather than on the production process, i.e. risk-driven enforcement focusing on the detention of potentially hazardous foods and feeds.

For enforcement of a process-based policy, it is necessary that event-specific methods are available for GMO events that have been authorised, and preferably also for GMO events that have not yet received authorisation. With the advent of gene-editing, this situation has become more nebulous, as it will not be feasible anymore to have event-specific methods for every gene-edited variety. Therefore, the direct link between the (non-event-specific) detection method for a particular edit and the safety dossier for a GMO with the same edit, is no longer guaranteed. As this gene-edit in one organism may likewise be produced in another, this also severely complicates the enforcement of GMO legislation in practice. This disconnect will also challenge the safety of the edited product, once the edit has been identified during enforcement. This is because a gene-edit that will modify a particular elite variety, strain, or breed, in a certain way, with a specific set of off-target modifications, may be produced again in a repeat experiment with the same modification, but with a different set of off-target modifications. Furthermore, the issue of the application of multiple modifications in the same trait-related sequence or sequences, has not been solved yet in terms of the detection methods that would need to be provided by the applicant: the requirement for a method for each modification will become very burdensome for applicants, but if methods are required for only a subset of the modifications, then the screening will become less (and less) informative. The above primarily relates to plants and animals. For plants, it may still be considered to link up to existing approval procedures, such as plant variety registration schemes, that may also include aspects of safety. This will possibly be the best guarantee for global harmonisation in the long term, but it is clear that this will be a long shot in practice.

For micro-organisms, targeted mutagenesis has been feasible for a longer period already, and thus it should be considered impossible to have GMO-specific methods for each novel micro-organism that has been obtained by gene-editing or other molecular biological tools. Likewise, it will usually not be feasible (yet) to have quantitative methods for GM micro-organisms. Here also, it seems prudent to develop methods that will be able to screen for the potential presence of GM micro-organisms that may seem undesirable in our food and feed or in the environment.

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## 1.3 Safety

With new gene-editing techniques being applied increasingly and with the expanding knowledge of the DNA basis of individual, economically relevant traits, it may well be assumed that the number of novel products produced with the use of gene-editing will rise, and that these products will be more diverse. The fact that small modifications are globally either not regulated, de-regulated after initial notification, or in practice not enforced, will significantly add to this effect, but it seems plausible that also larger modifications will move towards the world market in the years to come. These modifications may generally be modest, with the modification of single traits, but they may increasingly entail more profound changes in the organisms' physiology.

These developments do not entail risks in general: market parties will take the necessary precautions to ensure that their products are safe. At the same time, this expansion of new traits in agricultural and food producing organisms should be considered with care. Systems should be in place to monitor global developments adequately, enabling the timely identification of any development that will require further scrutiny. Safeguarding the European food and feed supply chains will rely on such systems more and more, as it will not be feasible to identify all unauthorised GMOs, including the gene-edited events, in standard monitoring programmes at the border or in the respective supply chains.

In the case of gene-edited GMO events, it will generally not be possible to have GMO-specific methods available, as part of the authorisation dossier, that will uniquely identify the particular GMO of that specific dossier. Accordingly, the feasibility to have effective programmes to distinguish approved from unapproved events will decline even when the intended modifications may be the same, the off-target modifications and related effects may differ in practice as a result of (slight) differences in the transformation procedure, for instance. The safety consequences of this may be limited, but it does alter the (basis of the) current authorisation procedure for GMO events, with the requirement of an identifying method directly linked to a safety dossier of a particular GMO, which will no longer be fully applicable.

Another development that can be observed, is the shorter developmental programme of new, modified organisms, be it plants, animals or micro-organisms. This may entail less scrutiny during a number of years to identify any unintended effects, should there be any. A more integral Safe-by-Design approach may make up for this loss of years of observation: if new organisms are assessed for hazards throughout the entire research and development programme – from initial project idea up to the final ready-for-the-market product – this seems the best guarantee for safe products, provided that all involved in the research programme are trained in Safe-by-Design and responsible-research-and-innovation. At the end of the research programme, this may result in a complete dossier underpinning the safety of the novel product or biological innovation, that likely provides all answers to safety questions that may be raised and will stand any external further scrutiny. Nevertheless, a more thorough pre-market assessment may still be justified if not all questions can be answered in this way.

In the case of animals, the health and welfare of the animal are regarded as the most important criteria for the quality of the derived animal products. This will not change in the future. For this reason alone, it is of importance to monitor these aspects carefully, also in view of the ongoing developments in animal breeding. If animals are bred for the production of specific bioactive compounds, this may likewise be the case, but here it is clear that strict segregation of these animals and related products should be guaranteed at all times. In micro-organisms and in plants there is a clear movement towards the use of chassis organisms that will allow orthogonal modifications that will not affect the organism as such. In animal breeding, this seems an unlikely scenario, here animal health and welfare issues will require careful attention at all times, out of safety considerations, but clearly also because of ethical issues and public acceptance.

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## 1.4 Economics

Because agriculture is an important part of the Dutch economy any changes in regulation of novel GMOs, including gene-edited varieties, may have far-reaching economic consequences, both for the Netherlands and for other EU member states. Policy makers may address the issues of novel technologies (e.g. gene editing) in different manners, the different scenarios indicated below and their economic implications are reviewed in a separate report (Annex 4), although the conclusions are incorporated below.

### 1. **Process-based approach I (current situation)**

Products developed by all novel breeding technologies (e.g. gene editing) are regulated according to the existing GMO regulatory framework. Products developed by radiation or chemical induced mutagenesis are exempted

### 2. **(Sub-scenario) Process-based approach**

Products developed by use of novel technologies that induce only small modifications or SNPs (that cannot be related to the use of modern mutagenesis techniques) are exempted.

### 3. **Product-based approach**

All products are (basically) assessed prior to entering the European market, comparable to the current Novel Foods approach where products that do not have a (confirmed) history of safe consumption may be assessed as novel foods products. Novel foods that are clearly different from products already on the market will require a pre-market safety assessment. There will be a grey area of products that may or may not be regarded as novel foods. It will need to be considered how to assess new plant/animal/microbial organisms for environmental safety.

### 4. **(Sub-scenario) Product-based approach**

An alternative approach for new plant varieties may be adherence to the UPOV regulations for new plant varieties and include safety aspects in the registration procedure. This may allow for global harmonisation of market approval of new plant varieties. It will need to be considered how to assess new animal and microbial organisms in a similar procedure.

The process-based legislation that is implemented by the European Union is mainly intended to handle uncertainty and safety issues regarding GMOs. Scientific research from the past years has provided a lot of knowledge about the novel technologies and their potential risk. Genetic alteration occurs all the time in nature and it therefore can take place with both novel GE as well as GM techniques. This potential risk could therefore account for both the novel as genetical modification techniques. According to the Directive 2001/18/EC, the product itself also has to be examined if a particular technique is used that is related to the EU GMO regulations. Therefore, a product-based approach is also used in the legislation. More products would be allowed under a product-based approach as the end-product is assessed instead of the whole process (Sprink et al., 2016). Also, the recent decision of the European Court of Justice has clarified that certain NBTs are genetic modification and that the resulting organisms hence fall under the regulations on GMOs (Wesseler et al., 2019). Various non-EU countries are already further in their development of these new techniques applied to plants, animals and microorganisms due to their less strict regulatory environment compared to the EU. This has major economic consequences as European countries, among which the Netherlands, might lose their leading position in the world market in the agricultural, livestock and microbial sector. Due to higher marketing costs, R&D concerning these new techniques moves out of Europe and gives other countries a competitive advantage. This mainly has an effect on smaller/medium sized European companies as they are less able to cope with the increasing costs for R&D or are not able to move part of their production process outside Europe. And even if companies move their research to countries with less strict regulations for GMOs, the export of these products remains an issue.

These novel techniques could also help to establish a circular economy and decrease pollution. Moreover, if certain techniques such as NPBTs do not fall under the GM regulations, the labelling requirements will become more simplified which reduces costs (Wesseler et al., 2019). It is therefore important for the EU to be less strict in their legislation towards GM techniques. This could be achieved by switching to a more product-based approach to assess the end products instead of the whole process that is necessary to derive these products. Products will still be regulated in this case, among other things by the European food law. This can also be noticed for other countries who already



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implemented a product-based approach and therefore have a less strict regulatory process. However, the success of this product-based approach is depending on how it will be interpreted. If the request for GMO product authorization would be more similar to the already existing novel food authorization, this would reduce time needed for the authorization process. The Commission has the authority to decide to place the products on the European market and if the product might have effect on human health, a risk assessment will be requested by EFSA. The standing Committee has to vote in favor of the product before it can be lawfully placed on the EU market. This process will also hold for products from a third country. Such a regulation will simplify and shorten the authorization process, and therefore make the process clearer for both producers in the EU and from outside the EU that are exporting their products to Europe. This will reduce costs these producers and increase the competitiveness of the European market.

## 1.5 Regulatory aspects

At this moment GMO-related legislation is primarily process-based, although some aspects have a somewhat more product-based character, for instance, whether the newly expressed product has already received approval for use in food and feed products. A product-based strategy will entail the assessment of all new plant, animal or microbial products, there can be no exception to this rule in a truly product-based legislative system. At the same time, this does not mean that all products will require the same scrutiny. In this respect, the comparison with the regulation of novel foods, that follows similar strategies in most countries worldwide, is relevant. Products that are derived from plants, animals or micro-organisms, or from chemical processes, that are significantly different from products already on the market, either because the source organism has changed, or because the process to obtain the product has been altered significantly, will require a safety assessment. This assessment may range from a theoretic assessment based on an initial scan to an extended risk assessment based on a full dossier. A similar approach may be followed for all novel organisms that have been altered genetically. This will entail a case-by-case approach where the latest insights in this rapid evolving field can be used to adequately assess the new organism for its specific safety characteristics. Additional safeguarding may be realised by actively requiring Safe-by-Design strategies throughout all phases of research and development for new organisms and other biological innovations. As all countries and regulatory aggregates struggle with these issues, it seems timely to invest in harmonisation of such a more general safeguarding system.

### **Regulatory aspects (expert interviews)**

During the interviews (see Annex 3, interviews Social Sciences) it was stated that governments struggle with the best way to deal with changes in (social) life due to technology, and to mitigate effects before they occur another type of assessment is needed, and this is wider than only gene editing technology. If a new technology, such as gene editing, is expected to be (very) powerful, the effects should be weighed in advance.

During the interviews, the experts were particularly asked to what extent the precautionary principle is affected by a transition from process-based to product-based regulations. For the EU, the precautionary principle is the primary principle, also in other fields besides biotechnology. And although there is some difference in interpretation between sectors, the aim is to protect public health and environment in case of an unknown risk, and to prioritize the protection over the internal market. One expert noted that under the precautionary principle (as laid down in e.g. European Commission document 2002/3), there is also the corollary requirement for the party taking the measures (in this case the EU) to take away the outstanding uncertainties regarding risks. Yet such proactiveness is lacking in the EU. The expert also noted that this may give rise to a perpetuum mobile as the discussion would then subsequently shift towards the political decision as to whether the reassurance gained through a science-based/precautionary approach would already suffice to proceed to approvals and exemptions. This expert also noted that harmonization of safety assessment requirements would still fail to address the current stalemate in the EU decision procedure, as the EU has various additional political voting rounds (as opposed to other nations) before approval is granted to market a GMO.

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The precautionary principle was also cited by the Court of Justice of the EU in the judgement on NBTs, and although it is science-based in core, it is often labelled as anti-scientific by adversaries. It implies that new technologies are something to worry about, which influences European perception.

How innovation is boosted or thwarted, will depend on the European Commission's final proposition for possible legal amendments and the phrasing of this new proposal, although one of the interviewees stresses that no new proposal will escape precautionary principle. As regards exemption of 'not-novel' products from the requirement for regulatory approval, one expert noted that, based also on the Canadian example, the concept of novelty has been ill-defined. Nonetheless, the Canadian authorities have a good internal attuning of their product-based legislation between the different sectors. In addition, there is the possibility for developers and innovators to consult with the authorities at a very early stage of product development on the regulatory status and possible risk assessment needs for their prospective products.

## 1.6 Social acceptance and public opinion

Social acceptance of both the safety testing approach and of the products approved are essential for successful commercialization for GM and gene-edited food products.

Since the commercialisation of the first GM crops in the 90s, application of biotechnology in the development of novel food products has come under much scrutiny. Opponents of GMOs have raised questions about diverging issues, such as the impact of the genetic modifications on the environment and food safety. Environmental issues include the potential cross-breeding of GMOs with related wild species, resulting in a GM variety with a competitive advantage. Furthermore, there are worries regarding the food safety of GM products among consumers, although there is no scientific evidence that currently authorised and commercialised GMOs pose a risk to food safety, as these have been extensively evaluated on a case-by-case basis prior to release on the market.

Surveys assessing the opinion towards GM foods have been conducted since the early 90s and have shown negative public attitudes toward GM foods in most EU countries. A comparison of the results from the European Commission's Eurobarometer surveys conducted in 1996, 1999, 2002 and 2005 showed that, overall, the support for GM foods declined over time (Gaskell et al., 2006, 2010). In the 2010 and 2019 Eurobarometer reports, the support for GM foods was not investigated by the EU survey. However, participants were asked which food safety topics concerned them. Around a quarter of the participating EU citizens (27%) are concerned about GM ingredients in food or drinks, as found in the latest Eurobarometer survey on food safety from 2019 (Kantar, 2019). In the 2010 survey, GM ingredients in foods and drinks was the fourth topic of which EU citizens were most concerned about the associated risks (TNS Opinion & Social, 2010).

The development of gene-editing techniques is more recent, and fewer information is available on the public acceptance of such techniques in (the) food (production chain). Only 4% of the participants are concerned about genome editing in the 2019 Eurobarometer (Kantar, 2019). However, genome editing has, of all topics, the lowest awareness score (21% of the survey participants had heard of genome editing before).

Within food-related GM applications, consumers are more negative when it comes to GM animal than GM crops (L.J. Frewer et al., 2013; Lynn J. Frewer et al., 2014). Application of animal biotechnology is more complex because of the difficulty to predict related physiological effects in the resulting GM animals, which may lead to unacceptable levels of pain or stress. These technologies may therefore not be readily accepted by the public, especially when genetic alterations are introduced in livestock mainly to benefit commercial interests. Further considerations that may influence public opinion are the unnaturalness of genetic alterations and the impact on the integrity of the livestock animals' life.

Surveys into the opinion of consumers towards GM foods, or their willingness-to-pay for GM (free) foods, indicate there is considerable variation between consumers. Factors (that seem to correlate with) attitude toward GM foods, with younger male consumers having a more positive attitude towards GM foods). Multiple studies show that within a certain consumer group, a subgroup of them is

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generally positive about GM (or gene-edited) food products, while other consumers are more hesitant and base their judgement on overall benefit and risk perceptions, and there often is a subgroup that is against GM's per se. Furthermore, public's acceptance of GM animal food products and GM plant food products differs worldwide (L.J. Frewer et al., 2013). North American and Asian consumers are more positive towards GM applications than European consumers (L.J. Frewer et al., 2013).

Information can be an important component in formation of the public's attitudes towards GM or gene editing. Experts in the field are more positive about the application of gene-editing in crops than lay public (Kato-Nitta et al., 2019), and the same is true for genetically engineered food (Scott et al., 2018). A recent study conducted in the Netherlands, UK and US demonstrated that knowledge of a GM technology is a unique predictor of the attitude towards GM food and changing the attitude (positively) can be achieved by teaching people about the science behind GM foods (McPhetres et al., n.d.). There is a positive relation between trust in scientist and regulatory authorities and a positive attitude toward GMO foods (Marques et al., 2015).

However, despite the opportunities for public education in altering the attitudes towards for products resulting from NBTs, it is unlikely that all consumers will judge them positively. At least for GM food, it is known that certain consumers see genetic modifications in food as a moral violation, and will be against it no matter the risks or benefits (Scott et al., 2018). Similarly, others have argued that factual information regarding the food safety of GM foods is not likely to influence all consumers, there is an emotional component in the disapproval of GM's (Mallinson et al., 2018).

This lack of acceptance by some consumers for GM products and products from NBTs, will likely also give a lack of acceptance for a more product-based approach in safety testing. Perhaps consumers should be given the opportunity make their own judgement about the GM and gene-edited food, in line with the value of free choice. Labelling products either with the GM, or gene-edited, or as GM- or gene-edited free, would give consumers the freedom to choose the type of products they approve. However, there are several downsides and practical issues that make labelling of (all) products very difficult. First, there is the traceability issue, as discussed, particular for products with gene-edited products. A labelling system may be costly, leading to increase prizes for the consumer (Scott et al., 2018). Moreover, labelling may lead to a certain stigmatization of the technology, negatively affecting overall acceptance of NBTs (Scott et al., 2018).

Momentarily, products bearing the label 'organic' ('biologisch'), are free from GM and gene-edited crops (and products thereof) (COGEM, 2019), enabling consumers to choose products and crops that are not made with these techniques. In the future, increased transparency in food chains may be a way to enable consumers to be informed about the production and origin (and use of GM or NBTs).

### **Social acceptance and public opinion (Expert interviews)**

Interviewed experts (see Annex 3, interviews Social Sciences) point out that there are polarised views in society towards modern biotech, and a large part of the consumers are not at all interested. This variety of views can be illustrated with the popularity of foods with a traditional (artisanal) image on the one side versus the popularity of functional foods, such as protein foods on the other side.

The experts observe difference in the perception of green, white, and red biotech. Green biotech is generally not well accepted, in line with the view of consumers towards food: romantic, no gene technologies needed. One of the underlying views is the concept of naturalness of food, whereby unnatural is considered bad. One of the experts also noted that some stakeholders may still view the introduction of natural mutations as a substantive manipulation of the host.

The public accepts red biotech, with the production of medical products, more than green biotech: consumers seem to be more prone to accept risk when diseased. However, the pharmaceutical industry and their intentions are distrusted. The white biotech, with industrial use of biotech is very unfamiliar by the general consumer, because there is little interest for it. This unawareness, possibly in combination with less relevance of environmental effects due to contained use, means less opposition to white biotech. In addition, one interviewee noted that there is a difference between the way that plants, microorganisms and animals ('cuddly') are viewed by the public. For animals, The

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Netherlands even make a further distinction between those used for experiments and those used for *e.g.* animal production (for which the 'no, unless..' policy applies). It is difficult, though, to single out particular animal species for protection from a legal point of view. Ethical considerations underlie the policy to allow for GM animals being used for medical experiments, yet despite giving insights into the concerns felt by the public, ethics will not give the answers to address them.

Other factors that influence perception of biotechnology is whether there is a benefit for the consumer (more acceptance), and the freedom of choice for consumers. One of the interviewees describes that the ambivalence towards technology, roots in the following overarching questions: 'Is the technology used for a good reason?', 'Can scientists and regulators be trusted, to weigh good and negative sides of technology (aka are they honest brokers)?', and 'What are consequences for stakeholders and ethics?'. Another expert noted that the trust in institutions is also a determining factor. Whereas many citizens do actually trust the governmental authorities, any mistakes and errands will greatly impact on this trust. The majority of the population is relatively inert nonetheless, with few or no associations whatsoever with the technology.

Furthermore, one of the interviewees points out that discussions on biotechnology are often reduced to technical risks, which leads to little space for negotiation. Moreover, technologists have a main role in these discussions, while they may be poorly equipped to answer the more overarching questions on ethics and on farming systems. Another expert noted that intuition may also be an important determinant in perception, whilst safety may not necessarily equate healthiness in the public eye. One of the experts gives the example of Norway, whereby both technical aspects and likely contributions to society and sustainability are weighed. Public dialogue should be wider than civil society groups.

In case of gene editing: some technical 'wizarding' (in legislation) may lead to a situation where edits do not have to be controlled, but is questionable if this is desirable for the public opinion. Another interviewee noted that participative methods, such as consensus conferences, used to be popular for some time, yet it has proved difficult to achieve consensus. Moreover, this participative deliberation actually had a limited role within the overall decision process. Expectations management is therefore advocated so as to avoid disappointment amongst the participating stakeholders.

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## 2 Sector specific document: Plants

### 2.1 Developments in the plant sector

New plant varieties that have been obtained with NBTs have received a lot of attention in national and international media (Malyska et al., 2016). The public interest may be accounted for by their association with food products. Initial applications relate primarily to small insertions/deletions (indels), whilst also homology-directed recombination (HDR) –based gene editing has been achieved in plant materials (several, including rice and tomato). Experimentally, it has been shown that it is possible to edit the same or different targets in multiple genomic locations simultaneously, allowing for more profound changes in the resulting plant varieties (Mao et al., 2019).

The range of traits that has been introduced so far by the using more conventional recombinant-DNA techniques is still rather limited, with a clear focus on herbicide tolerance and pest resistance, with stacks of both traits accounting for 45% of the total area planted to GM crops worldwide in 2019, for example (ISAAA, 2020). This range is, however, much more extended when also the experimental GM plants are included that have so far not reached the market, or only in a limited number of countries (Zhang et al., 2016). These traits relate to virus resistance, nematode resistance, improved nutritional and organoleptic characteristics, reduction of anti-nutrient compounds, increase of yield, prolonged shelf life, altered phenotypes, and many others. Because the use of NBTs may to a large extent remain unnoticed, for instance due to exemption from regulatory oversight in exporting countries and lack of detectability in imported consignments inspected at the border, this may result in an increase of imports of unauthorised GMOs compared to what has been observed in the European Union so far.

Examples of plants with traits modified by gene editing that have already received market approval in other countries can be found in Table 1. Besides Disease resistance and herbicide tolerance, also other traits have been edited resulting in different plant composition, different stress tolerance, and increased yield, amongst others

### 2.2 Latest developments

The application of synthetic biology is generally regarded as a future development, but Selma et al. show that the use of plants for specific purposes by 'rewiring plant metabolic and developmental programs with orthogonal regulatory circuits' may be feasible in the near future (Selma et al., 2019). In their paper they describe the use of synthetic transcriptional activators that are based on CRISPR-Cas9 architecture and because of this can easily be applied for use in synthetic biology pathways by their ability to activate different promoters.

Chen et al. (Annual Review of Plant Biology, March 2019) describe how plant breeding programmes will be shortened by 4 – 8 years, depending on the crop (K. Chen et al., 2019). They describe many ways of applying nuclease-based genetic tools, using DNA or DNA-free transient expression systems, to modify crop plants based on single as well as more complex genetic modifications. These developments may lead to the application of synthetic biology in plants, including the use of crop plants as broader production organisms, to accelerated domestication of wild plants of interest (the rapid domestication of the groundcherry was recently published as an example), as well as future developments that will reduce off-target effects and lead to increased efficiency of homology-directed repair, which will effectively open up the route to more detailed metabolic adaptations of the plants. Khan et al. similarly describe how the use of CRISPR-Cas14a, that can cleave single-stranded DNA, may specifically act against single-stranded DNA viruses in crop plants (Khan et al., 2019).

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### **Developments (Expert interviews)**

In the expert interviews (see Annex 3, Plant Interviews), gene editing methods, in particular CRISPR-Cas, are mentioned frequently as most important development in the sector. In this context, the separation of research and production is mentioned very often: gene editing is used for research purposes (for example to study the effect of particular genes) while for production plants are selected that have the same mutation obtained through conventional breeding methods. Another important development mentioned is the overall quicker development of new breeds, due to the application of various novel techniques. Not only gene editing is mentioned in this context, but also the use of DNA markers (marker assisted selection), whole genome sequencing (WGS), robot-phenotyping (big data, automated analysis). The findings of fundamental research can nowadays more easily be used in plant breeding, owing to the technological progress.

Currently, the focus is on complex traits, influenced by multiple genes. Gene editing can be used to create diversity, although this is mainly something occurring within companies and institutions outside the EU. Another development mentioned is the change from conventional transgenesis to CRISPR-Cas mutagenesis, particular for silencing genes. An explicit example that was given was about genes involved in the susceptibility to pathogens. When silenced, this can lead to a more resistant plant, reducing the need for the use of pesticides.

Some critical notes were made as well, for example from the vegetable sector: for certain vegetables, it is technically difficult to apply NBTs.

What was indicated as an important beneficial development is the overall increase in the speed of developing new breeds, whereby breeders can more quickly develop breeds/plants that fulfil the (rapidly changing) wishes of consumers and society (ease of use, sustainability, reduction in agricultural use of chemicals). One interviewee stated that CRISPR-Cas mutagenesis may be accepted more by consumers.

In the interviews no particular developments of concern were indicated, whilst some interviewees mentioned that gene editing can actually reduce occurrence of unwanted effects even further, compared to conventional breeding methods.

**Table 1** GM crops based on gene editing that have already received market approval in the USA and Canada (organised by trait category)

Trait category	Species	Type of modification	Trait	Petitioner (website)	Country	Authority	Status	Year
Breeding technology	Plants	Centromere-mediated chromosome elimination	Cytoplasmic male sterility	New Zealand Institute for Plant and Food Research	USA	USDA APHIS	de-regulated	2011
	Plum	Null-segregants from transgenic, early-flowering plum plants	Early flowering	USDA ARS	USA	USDA APHIS	de-regulated	2011
	Potato	CRISPR-Cas9	Self-compatibility	Simplot Plant Sciences	USA	USDA APHIS	de-regulated	2020
	Setaria viridis	CRISPR-Cas9	Delayed flowering time	Donald Danforth Plant Science Center	USA	USDA APHIS	de-regulated	2017
	Tobacco	Null-segregants from transgenic, early-flowering tobacco plants	Early flowering (to accelerate breeding)	North Carolina State University	USA	USDA APHIS	de-regulated	2011
	Tobacco	Null-segregants from transgenic, early-flowering tobacco plants	Early flowering (to accelerate breeding)	Arnold and Porter, LLP	USA	USDA APHIS	de-regulated	2015
Composition	Alfalfa	TALEN	Low lignin (improved nutritional quality)	Calyxt	USA	USDA APHIS	de-regulated	2017
	Camelina	CRISPR-Cas9	Increased oil content, improved oil stability (mentioned on applicant's website, not in correspondence with USDA APHIS)	Yield10 Bioscience	USA	USDA APHIS	de-regulated	2017
	Camelina	CRISPR-Cas9	Increased oil yield (through increased fatty acid biosynthesis and diminished oil body turnover)	Yield10 Bioscience	USA	USDA APHIS	de-regulated	2018
	Canola	CRISPR-Cas9	Altered oil composition (not specified)	Yield10 Bioscience	USA	USDA APHIS	de-regulated	2020
	Canola	Oligonucleotide-directed mutagenesis (Rapid trait development system)	High-oleic acid	Cibus	USA	USDA APHIS	de-regulated	2020
	Canola	CRISPR-Cas9	Enhanced protein, low glucosinolate, and low phytate	Corteva	USA	USDA APHIS	de-regulated	2020
	Coyote tobacco	CRISPR-Cas9	Lack of nectarin (superoxide dismutase) proteins in floral nectar	Max Planck Institute	USA	USDA APHIS	de-regulated	2019
	Maize	CRISPR-Cas9	Starch exclusively containing amylopectin	DuPont Pioneer	USA	USDA APHIS	de-regulated	2016
	Maize	Meganuclease	Increased starch	Agrivida, Inc.	USA	USDA APHIS	de-regulated	2015
	Nicotiana glauca	CRISPR-Cas9	Lack of different cuticular lipid components of the seed	Weizman Institute	USA	USDA APHIS	de-regulated	2020
	Pennycress	CRISPR-Cas9	Reduced erucic acid	Illinois State University	USA	USDA APHIS	de-regulated	2018
	Pennycress	CRISPR-Cas9	Seed pigmentation: mutation caused by CRISPR in the tt8 gene, which codes for the TT8 transcription factor controlling seed pigmentation	Illinois State University	USA	USDA APHIS	de-regulated	2019
	Potato	CRISPR-Cas9	Reduced glycoalkaloid content	Simplot Plant Sciences	USA	USDA APHIS	de-regulated	2020
	Potato	CRISPR-Cas9	Reduced glycoalkaloid content & suppression of polyphenol oxidase (prevention of blackspot)	Simplot Plant Sciences	USA	USDA APHIS	de-regulated	2020



Trait category	Species	Type of modification	Trait	Petitioner (website)	Country	Authority	Status	Year
	Potato	CRISPR-Cas9	Reduced content of reducing sugars after storage (by inhibition of vacuolar invertase activity), preventing browning and acrylamide formation during heat processing	Simplot Plant Sciences	USA	USDA APHIS	de-regulated	2020
	Soybean	TALEN	High-oleic acid soybean	Collectis Plant Sciences	USA	USDA APHIS	de-regulated	2015
	Soybean	TALEN	High-oleic acid soybean	Collectis Plant Sciences	USA	USDA APHIS	de-regulated	2015
	Soybean	TALEN	High-oleic/low-linolenic acid soybean	Calyxt	USA	USDA APHIS	de-regulated	2020
	Soybean	CRISPR-Cas9	High-oleic acid soybean	ToolGen	USA	USDA APHIS	de-regulated	2020
	Soybean	CRISPR-Cas9	Altered seed composition (not specified)	University of Missouri	USA	USDA APHIS	de-regulated	2020
	Soybean	CRISPR-Cas9	Increased oil and protein contents	Corteva	USA	USDA APHIS	de-regulated	2020
	Tobacco	Meganuclease	Nicotine-free	North Carolina State University	USA	USDA APHIS	de-regulated	2017
	Tomato	CRISPR-Cas9	Increased gamma-aminobutyric acid (GABA) content	SanaTech Seed	USA	USDA APHIS	de-regulated	2020
	Wheat	TALEN	High fiber content	Calyxt	USA	USDA APHIS	de-regulated	2018
Disease resistance	Canola	Oligonucleotide-directed mutagenesis (Rapid trait development system)	Fungal resistance (not specified)	Cibus	USA	USDA APHIS	de-regulated	2020 (7x)
	Citrus trees	CRISPR-Cas9	Citrus canker resistance	University of Florida	USA	USDA APHIS	de-regulated	2020
	Maize	CRISPR-Cas9	Northern Leaf Blight resistance	DuPont Pioneer	USA	USDA APHIS	de-regulated	2018
	Plasmids	Transient expression	Antifungal (application of plasmids to plants; transient expression), particularly against crown rot in tomatoes	Rutgers University	USA	USDA APHIS	de-regulated	2014
	Rice	TALEN	Resistance to bacterial blight caused by <i>Xanthomonas oryzae</i> pv. <i>Oryzae</i>	Iowa State University	USA	USDA APHIS	de-regulated	2015
	Rice	CRISPR-Cas9	Bacterial blight resistance	University of Missouri	USA	USDA APHIS	de-regulated	2020
	Soybean	Gene editing (not specified, leading to a knock-out mutation)	Resistance to soybean cyst nematode	Evogene	USA	USDA APHIS	de-regulated	2020
	Tomato	CRISPR-Cas9	Herbivore insect resistance	Michigan University	USA	USDA APHIS	de-regulated	2020
Herbicide tolerance	Wheat	TALEN	Mildew resistance	Calyxt	USA	USDA APHIS	de-regulated	2016
	Canola	Oligonucleotide-directed mutagenesis (Rapid trait development system)	Tolerance to tribenuron-methyl and thifensulfuron-methyl herbicides	Cibus	Canada	CFIA	plant with novel trait	2013
	Canola	Site-directed mutagenesis	Tolerance to imazamox and imazapyr herbicides	BASF	Canada	CFIA	plant with novel trait	2014
	Canola	Oligonucleotide-directed mutagenesis (Rapid trait development system)	Tolerance to herbicides (not specified)	Cibus	USA	USDA APHIS	de-regulated	2020
	Flax	Oligonucleotide-directed mutagenesis (Rapid trait development system)	Tolerance to herbicides (not specified)	Cibus	USA	USDA APHIS	de-regulated	2020
	Rice	Oligonucleotide-directed mutagenesis (Rapid trait development system)	Tolerance to herbicides (not specified)	Cibus	USA	USDA APHIS	de-regulated	2020; 2020
Quality	Avocado	CRISPR-Cas9	Prevention of fruit flesh discoloration (by suppression of polyphenol oxidase)	Simplot Plant Sciences	USA	USDA APHIS	de-regulated	2020

Trait category	Species	Type of modification	Trait	Petitioner (website)	Country	Authority	Status	Year
	Barley	CRISPR-Cas9	'Naked caryopsis' phenotype, which allows for easy removal of the seed hull during threshing (preferred for processing for human consumption)	Oregon State University	USA	USDA APHIS	de-regulated	2020
	Lettuce	Unknown	Anti-browning (no details of modification, except for 'deletion'; other products from the same company such as Arctic Apple target the genes encoding polyphenol oxidase)	Intrexon	USA	USDA APHIS	de-regulated	2019
	Mushroom	CRISPR-Cas9	Anti-browning	Penn State	USA	USDA APHIS	de-regulated	2016
	Mustard	Genome editing (not specified)	Suppression of formation of pungent compounds	Pairwise	USA	USDA APHIS	de-regulated	2020
	Pea	CRISPR-Cas9	Improved flavor	Benson Hill	USA	USDA APHIS	de-regulated	2020
	Petunia	CRISPR-Cas9	Flower color	ToolGen	USA	USDA APHIS	de-regulated	2020
	Potato	TALEN	Enhanced product quality (not further specified)	Cellectis Plant Sciences	USA	USDA APHIS	de-regulated	2014
	Potato	TALEN	Reduced black spot	Calyxt	USA	USDA APHIS	de-regulated	2016
	Potato	TALEN	Reduced black spot / PPO	Simplot Plant Sciences	USA	USDA APHIS	de-regulated	2016; 2020
	Tomato	CRISPR-Cas9	Lack of pedicel abscission (clean detachment from plant during harvest)	University of Florida	USA	USDA APHIS	de-regulated	2018; 2020
Stress tolerance	Maize	CRISPR-Cas9	Drought tolerance and yield stability	Corteva	USA	USDA APHIS	de-regulated	2020
	Soybean	CRISPR-Cas9	Drought and salt tolerance	USDA ARS	USA	USDA APHIS	de-regulated	2017
	Soybean	Epigenetic reprogramming (null-segregant)	Modulation of defence and stress response	University of Georgia	USA	USDA APHIS	de-regulated	2018
	Soybean	Epigenetic reprogramming (null-segregant)	Modulation of defence and stress response	Epicrop Technologies	USA	USDA APHIS	de-regulated	2017
Yield	Canola	Oligonucleotide-directed mutagenesis (Rapid trait development system)	Pod shatter reduction	Cibus	USA	USDA APHIS	de-regulated	2020
	Maize	Meganuclease using a DNA repair template	Enhanced photosynthetic efficiency and/or capacity	Benson Hill Biosystems	USA	USDA APHIS	de-regulated	2015
	Maize	Unknown ('genome editing elements')	Increased yield	Benson Hill Biosystems	USA	USDA APHIS	de-regulated	2018
	Maize	CRISPR-Cas9	Increased grain yield	Corteva	USA	USDA APHIS	de-regulated	2020 2020
	Plants	Epigenetic effect in null-segregants from transgenic plants	Biomass, growth rate, yield, height, and others	University of Nebraska Lincoln	USA	USDA APHIS	de-regulated	2012
	Soybean	CRISPR-Cas9	Altered leaf size and seed weight	University of Missouri	USA	USDA APHIS	de-regulated	2020
	Strawberry	CRISPR-Cas9	Remontancy (bearing fruit multiple times a year)	Simplot Plant Sciences	USA	USDA APHIS	de-regulated	2020
	Tomato	CRISPR-Cas9	Reduced flowering time and increased compactness of the plant (more suitable for urban farming)	Cold Spring Harbor Laboratory	USA	USDA APHIS	de-regulated	2020

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### Timeline for moving to the market (expert interviews)

Gene edited plants, processed into food products from outside the EU where gene editing is judged differently, are most likely to appear on the European market, particular when the edits concern small edits or base edits (see Annex 3, interviews Plant Interviews). Also, non-food products and animal feed with gene edited plants (with minor changes) are likely to come to the market. Overall, the experts found it difficult to indicate a specific timeframe for edited plants moving to the market. One expert stated that this would likely occur within 3 years. Currently, imported feed already consists of GMO soy and corn, which are authorized for cultivation elsewhere.

The European procedures are considered to delay the appearance on the market severely. Also, the developments in the European parliament with regards to gene-editing legislation, are considered to be important determinants for this timeline.

Synthetic biology-derived plant products are not expected in the short term.

## 2.3 Traceability issues

So far, traceability aspects of GMOs have focused on GM plant varieties. For new GM plant varieties that move towards the European market, producers have the obligation to supply an event-specific method that meet specific minimum method performance requirements and linked to this, to supply positive and negative plant materials. These latter materials will be used in the subsequent European validation of the detection method by the European Reference Laboratory for GMO methods (EURL), the Joint Research Centre in Ispra, Italy, together with the European Network of GMO Laboratories (ENGL). Once this method has been validated and the GMO event is approved, this method will serve to enforce the European GMO legislation. At the same time, strategies have been developed to identify unauthorised GMOs, that may differ per member state, but that are all based on screening steps using genetic elements that are generally associated with GMO events, and combinations thereof may indicate the likely presence or absence of unauthorised GMOs in a particular product batch.

With the advent of the gene editing NBTs, these strategies will become less straightforward. It is generally acknowledged that it will be challenging to impossible for applicants to provide event-specific methods as part of the dossier that will meet the minimum performance requirements in terms of, particularly but not only, specificity: other breeders may set up breeding schemes, legally or illegally, that may result in the same modifications and enforcement laboratories will not be able to distinguish both events (ENGL, 2019). The re-establishment of the same trait using CRISPR-Cas procedures may be achieved by non-homologous end-joining (NHEJ) but increasingly more directly by larger transformations using HDR strategies. Also, it may be assumed that specific traits will increasingly be based on different types of modifications in the same gene(s). This will make it more challenging to develop informative screening strategies for specific traits.

This was illustrated in 2020, where Chhalliyil et al developed a PCR-based method that can detect and quantify a SNV in the AHAS gene that confers herbicide tolerance in canola (Chhalliyil et al., 2020). Although this particular SNV was introduced by gene editing, the published method does not prove that the modification resulted from genome editing (ENGL, 2020)). In addition, the European network of GMO laboratories (ENGL statement 2020) state that it is not validated for all criteria of a GMO testing method, such as the applicability and specificity for GMO's have been proven.

Thus, ENGL reports that there are no procedures that can establish with certainty that alterations result from SDN-1 gene editing, and that validation of event-specific methods is only feasible for SDN-3 genome-edited plants (ENGL, 2020).

In the case of multi-editing, it is not yet clear yet, how this will affect current views on the methods that will need to be supplied by the applicant. So far, a single method was sufficient to identify the event, also in those cases where it had been established, or could not be excluded, that there were additional (partial) integrations. In the case of stacked GM events, the underlying events would require separate approvals (except for re-transformed GM varieties), and thus for all underlying

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events in a stacked GM event crop plant methods should be available. In the case of multi-edited events, this would lead to the requirement for the applicant to supply as many methods of detection as there are edits. On the other hand, if a single method would suffice, and segregation of the individual edits would thus be accepted, all other edits may show up in any (mixed) plant material, and will be acceptable implicitly, and the definition of (un)authorised GMOs will likely become blurred. Moreover, in that case it is not clear what the consequence of segregation may be as this may lead to different phenotypes.

When considering a more product-based strategy, it is clear that it will be impossible to identify every new product at the border. Detection and identification will only be feasible on a risk-based approach by focusing only on those traits that are potentially risky.

### **Traceability (expert interviews)**

The experts indicate that traceability of gene edits is very different than of current transgene events, as it is not possible to develop event-specific methods for small modifications (see Annex 3, interviews Plant Interviews). It is not possible to prove what technique has been used for small mutations. In addition, some interviewees question if it is desirable to make event-specific DNA barcodes.

For internationally operating companies, there will be problems as well; the example is given for the use of materials or lines from certain regions/ countries with a more progressive view on regulation of gene edited organisms (such as Argentina) which will be problematic, because it will not always be clear what is the background of the material/line in question. Overall, in chains from floriculture plants are traced from start material to retail, so in that way it is possible to trace the plants.

The experts think that it may be technically feasible to trace specific traits: specific locations in the genome can be multiplied by PCR and sequenced; specific primers will have to be developed for all targets. However, these do not show if a mutation has been achieved with a new technique or with traditional mutagenesis (or spontaneously occurring).

## **2.4 Safety issues**

With the relative large variety of new traits that has already been the subject of experimentation in novel plant breeding, it may be foreseen that the range of products with altered characteristics as a result of the application of NBTs that may reach the European market may also be considerable. There is, however, no a priori reason to assume that the toxicological character of these new food or feed products will pose a risk to consumers or animals. Reasons, however, to be vigilant to some extent, is the fact that i) the new techniques may allow modifications on a scale that we have not seen so far, including the transfer, or even new introduction, of complete metabolic routes, entailing the introduction of new proteins as well as derived secondary metabolites, ii) plants are well known for their anti-nutrient and natural toxin compounds and thus harbour the metabolic networks to express such compounds that may be relatively easily amplified or modified in ways that are adverse to human and animal health, and iii) modifications are often aimed at achieving (insect) resistance and these modifications may, at least theoretically, be more relevant to human health compared to many other types of modifications.

Another safety aspect relates directly to the fact that it will not be feasible anymore to have 'real' event-specific methods for new NBT-based GMOs. The consequence of the presence of the same gene edit and related traits in authorised GMOs and unauthorised GMOs is that, while in both cases the toxicological characteristics related to the newly introduced trait, the intended effect, are likely to be the same, the potential unintended effects may differ. The reason for this is that the two procedures to come to a particular gene edit may differ, in one case the off-target effects may be very limited and well-characterised, while in a second programme there may be considerable off-target effects that may have potential adverse effects for humans, animals or the environment. Although this cannot be directly considered a major risk to the safety of our food supply, it does mean that the current approval system requiring applicants to provide a dossier consisting of a safety dossier for a new GMO in combination with an event-specific GMO method to trace this GMO in our food and feed supply

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chains, can no longer form the basis of our market approval system. This will also have consequences for our system of pre-market safety assessment.

When focusing on off-target effects of the application of NBTs in plants: the effects thereof are likely to be limited as the selection and removal of underperforming plants is standard practice in plant breeding, and in all cases a number of subsequent rounds of conventional (back)crossing will likely occur that will reduce the number of unintended effects in the specific plant's genome considerably. The widely acknowledged history of safety of these standard practices as applied to chemical and irradiation mutagenesis can be considered a positive attribute of the final crop plant product. At the same time the reduced number of generations that will be grown prior to the market stage when using more precise methods of mutagenesis may be considered a concern, also in the case of accelerated domestication of food crops. It will need to be monitored whether this may lead to an increased number of unintended effects in crop plants, and derived products, on the market.

More in general, although the chances that new plant products obtained by the use of NBTs will have adverse effects should not be exaggerated, and it is not so easy to turn a safe crop plant into an unsafe crop plant. Nonetheless, it seems prudent to i) carefully monitor global developments in this field and ii) to develop methodologies to screen for specific traits that are identified as possibly adverse to humans, animals or the environment (OECD, 2021) and iii) to set up strategies to assess off-target effects in the early stages of plant breeding programmes in a Safe-by-Design approach (Van der Berg et al., 2020).

As a means to prevent or reduce risks, both for consumers as well as production animals, Safe-by-Design principles may be incorporated in the development cycle of novel plant varieties (Van der Berg et al 2020). Safe-by-Design aims to instil a safety culture via the application of safety considerations throughout the early stages of ideas, design and R&D up until market release of a new product. At every stage of the production cycle assessments are carried out to monitor plant breeding steps performed, identify related hazards, perform further hazard characterisation, where applicable, and possibly initiate mitigation strategies that may include the timely adjustment of the breeding programme.

### **Safety issues (Expert interviews)**

Most experts do not see major safety issues when considering new gene-edited crop plant varieties (see Annex 3, interviews Plant Interviews). One of the experts stated that marketing CRISPR-Cas enables faster domestication of interesting (wild) plants – in these cases there is less known about the background of a plant, thus a focus on compounds with negative effects could be important in that case. A focus on compounds with negative effects is also important for other, more conventional, crops; although it has to be stated that there it is already a point of attention, and there is sufficient knowledge on the underlying metabolic routes. It is suggested that OECD consensus documents can be important guidelines for safety testing.

Overall, most interviewed experts indicate they have no concern regarding unintended effects. The reason is the comparison with current methods, where no regulations are in place, while unintended effects are considered to occur more. In current mutation breeding (such as with ethyl methanesulfonate, 'EMS') 99.9% of the effects are unintended, and this is out of balance with NBTs where there are hardly any unintended effects. Classic mutagenesis and crossbreeding with wild varieties, can lead to 10.000 to 100.000 SNPs. The breeder solely checks for unwanted phenotypic consequences and selects the mutant with the desirable phenotypic changes. Mutagenesis breeding lead to many mutations. However, they have been marketed without safety testing, due to the argument of 'a long history of safe use', which means no issues with safety are known. The fear that there are now issues, is considered strange by most of the experts. One of the interviewees indicated that the concern about the intended effects was because, with time, intended effects may get more 'exotic'. It is stressed that this should be very different than for medical applications (side effects are very important in such applications).

When the experts are asked for segregation of edits and safety concerns, the interviewees indicate that segregation of polygenic properties also occurs in plants obtained with 'regular' breeding

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methods. When you register a new variety, you have to show that properties are stable. One of the interviewees indicates this is not a particular additional safety concern. Another indicates that segregation should be a point of attention.

Basic requirements that should be met (when moving to a product-based approach), should be similar to what is already demanded, such as a plant free of toxins. Safety assessments should be realistic, proportional, and science-based. Current requirements for safety of GMO's is largely the result of the general dismissal of people against GM techniques, not risk-based. One of the interviewees stressed that knowledge on mechanisms is important, and illustrated this with an example: resistance for cyst nematodes in potatoes can be linked to a toxic mechanism, therefore this knowledge can help to monitor for the possible change in toxin contents.

## 2.5 Economic aspects

Plant breeding is a highly important sector for the Dutch economy and economic perspectives.

Current developments indicate that the application of NBTs focuses on programmes outside of Europe, with the activities within Europe generally reduced to a minimum. The current process-based legislation, requiring the same large amount of data for any new GMO, will jeopardise the competitiveness of the Dutch breeders in the international field already in the short term. A more product-based strategy, focusing specifically on safety, nutrition and environmental aspects in all phases of the breeding programme, on the other hand, may allow for a responsible introduction of related products to the European market and may benefit Dutch plant breeding by providing an extra quality label to the related products.

Similarly, current global segregation between different regulatory strategies for the market approval of products from new breeding techniques will likely result in an increasing number of import issues. Extra hurdles for the import of raw materials will negatively affect the European economy at large. The extent of these effects will require further investigations.

At the same time current developments in plant breeding may also offer new possibilities for the sector. There seems to be global concern over the potential of the new gene editing technique in food applications. If Dutch/European crop plant products can show that European plant breeding companies have breeding programmes with built-in well-established risk assessment strategies this may further add to quality perception of Dutch/European products, this may benefit the sector, especially in times to come when more major modifications and, for instance, synthetic biology applications may become more standard.

### **Economic aspects (expert interviews)**

An important opportunity is that development of new varieties could be much quicker with CRISPR-Cas than with current methods (see Annex 3, interviews Plant Interviews). As an example one of the interviewees describes that a mutation for sweet tomatoes could be introduced in about a year in an existing variety with CRISPR-Cas, while it would take multiple years (even up to decennia) to obtain this by cross breeding. For the floricultura, the sector is looking genetic solution that is future proof, particular to meet sustainability gains. This is difficult to achieve with current methods, and NBTs may be a solution. When products have very clear consumer or environmental benefits, this may benefit consumer and retail acceptance. Regular methods can be used to make such products, but that will be too slow.

A concern that is mentioned by some experts, is the situation whereby only large companies can market GM and gene edited plants and crops. The overregulation leads to less opportunities for smaller companies, there are limited opportunities for innovative start-ups that can use NBTs in Europe, while for example in USA there are much more opportunities. Dutch breeders may lose their current position.

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In the long run, some experts think that the green sector will become smaller, students may go abroad or change to red biotech. Breeders may move from Europe; certain large companies decided already after European court decision to move innovation. European may no longer be able to compete on the world market. Mixing regular and NBT-adapted crops could be a major risk, for example when a non-governmental organisation finds that it is accidentally marketed. Overall, experts expect that not all economic activity will move soon.

Experts from companies are concerned about the public opinion regarding gene editing, and (want) to take different groups (consumers, farmers, supermarkets, processing companies) along in the discussion. The current position of only large companies marketing GM products not favourable in this aspect. If products from outside Europe could reach European market, this could be negative for European breeders. Another problem is that genes can be patented (in the US).

## 2.6 National / EU / global (regulatory) aspects

Different considerations apply when considering current developments at the national, the EU or the global level. National considerations relate to the importance of the sector for the Dutch industry, and may relate to specific concerns in some cases with relation to the Dutch environment. For the European context similar considerations may apply on a European level, here considerations of food or feed safety may be relevant in exceptional cases.

In both cases these aspects are directly related to the potential to be able to identify GMOs at the border. So far, all EU member states have monitoring programmes to analyse food, feed and seeds for the presence of authorised GMOs and, in most countries to a limited extent, for the potential presence of unauthorised GMOs. These programmes, if continued in their present forms, will not be effective to identify the new generation of GMOs. As it will be difficult to develop equally effective monitoring programmes for all categories of GMOs in the near future, it seems necessary to consider alternative options in this respect.

On a global level, the main overall interest seems to be to harmonise risk assessment strategies as much as possible in a way that will best guarantee the safety of innovative plant products for humans, animals and the environment, without stifling innovation by overly burdensome regulatory requirements. One option in this respect may be to link up to already globally harmonised frameworks, such as principles and guidelines as formulated by United Nations Food and Agriculture Organisation (FAO), or by the International Union for the Protection of New Varieties of Plants (UPOV), where the latter could cover aspects of both food and feed, but also environmental safety.

When considering a more product-based approach, it is clear, with the speed of innovations in the plant sector as provided in Table 1, that it will not be possible to assess all products from new plant varieties at the border. It seems more realistic to assume that the situation will become more in line with the approval system of novel foods in Europe, and elsewhere. This would mean that producers will have to apply for market approval for new foods and food ingredients that are significantly different from the products that are already on the market. The decision whether a particular product is a novel food lies primarily with the producers, but once a product is on the market, the food safety authorities may also determine that a product should (have) be(en) assessed under the Novel Foods regulations. The consequence is that there is a considerable grey area of products that may or may not be considered novel. At the same time, there are clear options for producers to discuss the safety aspects of their new products and there are legal options to remove products from the market should there be any concern about a particular product. An alternative strategy may link up to, as mentioned, the global UPOV-based plant variety registration: if safety aspects could become an inherent part of the registration procedure, this may provide the best overall strategy to guarantee the safety of crop plants. At the same time, it is clear that this will not be realised on the short term and, given the fact that different regulatory authorities have already taken steps to deregulate at least part of the novel food crops, it may become more difficult to include safety as a basic criterion for the registration of new crop plants. On the other hand, this strategy may still prove most (cost-)effective for plant breeders and food safety authorities similarly in the long run.



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### **Regulatory aspects (expert interviews)**

Experts think that when breeders are responsible for the product they market, they will ensure their product is safe (see Annex 3, interviews Plant Interviews). Safety should be guaranteed, but not at any costs. Experts say that safety assessments should be feasible. Product-based and science-based safety assessments can be an improvement, depending on how everything is specified. Science-based can still lead to very heavy safety dossiers, for example when every new metabolite should be tested. This will hinder progress, and in the long run it may endanger food security.

A difference between safety assessment and labelling, is currently not or hardly made. One of the experts claims that this enables consumers to reject novel techniques based on their convictions or emotions because they have the opportunity to choose. A 'biologic' or 'dynamic' label could be useful. An option would be to enable consumers to choose GM (and editing free) crops, for example via a particular label.

Currently, developers are proud of their products and publish in scientific journals. One of the experts fears this may change soon, and the developers are reluctant to make findings public, so traceability of new NBT-derived products is reduced.

Globally, many parts of the world invest in gene-editing, in Russia for example. In other parts of the world, scientists and authorities may be pleased with the little changes of development in Europe. One of the experts stresses that harmonisation is important, but that the EU should have done this earlier. The expert pleads that harmonisation should be done among states that are progressive towards gene editing (Japan, Australia, Argentina and possibly USA) and the EU.

## **2.7 Social acceptance and public opinion**

There is a difference in the perception between GM products obtained by cisgenesis and transgenesis among European citizens. A survey among citizens from 5 different EU countries (Belgium, France, the Netherlands, Spain and the UK) conducted in 2013 showed that the public's opinion about GMOs differs between cisgenic and transgenic products and EU citizens may accept cisgenic products more readily than transgenic food products (Delwaide et al., 2015). Consumers are more willing to accept cisgenically bred crops than transgenically bred crops, yet consumers still have preference for traditional bred crops ((Edenbrandt et al., 2018; Gaskell et al., 2010). Nevertheless, a more recent willingness-to-pay survey reports that consumers (among others respondents from Belgium and France) valued CRISPR gene-edited plant products similar as GM-derived products (Shew et al., 2018).

When the (perceived) benefits are large, outweighing negative attitudes and (perceived) risks, consumers may judge the GM food positively (L.J. Frewer et al., 2013). It is uncertain if the public would see agricultural benefits, such as larger yields, draught or pest resistance, as persuasive enough to judge GM plants positively (Mallinson et al., 2018).

Applying the responsible research and innovation (RRI) approach in the plant sector may improve social acceptance of crops produced with NBTs. RRI is a broad framework that considers the potential impact of research and development on the society at large with the aim to generate more value for users and society.

### **Public perception (expert interviews)**

Consumer acceptance of NBT is important (see Annex 3, interviews Plant Interviews). The experts point out that there should be dialogue between the sector and the consumers, as most consumers want to know how their food is produced.

It is stated that large companies now market the GM plants, which has no positive influence on the debate. In addition, the experts characterize GMO discussions as polarized and out of control. Some interviewees indicate that consumers should be made aware of processes, and both positive and negative effects.

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## 3 Sector specific document: (Livestock) Animals

### 3.1 Introduction

Animal biotechnology is a rapidly developing field, technologies such as genetic modification and cloning began in the 1980s, and have evolved since then. More recently gene editing methods have been introduced in modern animal breeding schemes in a number of countries. Application of animal biotechnology in general may serve different purposes. In recent years in scientific literature, examples can be found of genetically modified animal breeding to create model organisms to study human diseases, as well as the utilization of genetically engineered animals for the production of biopharmaceuticals, or indeed to increase animal production characteristics, that may include disease resistance. Examples of husbandry animal disease models include, amongst others, pigs with a disrupted CFTR gene to model cystic fibrosis (Rogers et al., 2008), a porcine tumorigenesis model (Sieren et al., 2014) and an ovine model to study Huntington's disease (Jacobsen et al., 2010). Furthermore, there are already a number of substances on the world market that have been obtained from GM animals, such as anti-thrombin alfa from goats (EMA, 2018; FDA, 2008) and sebelipase alfa from transgenic chicken (EMA, 2017; FDA, 2015a), amongst others. The first GM fish, the AquAdvantage salmon from AquaBounty Technologies, received market approval in the United States in 2015 and in Canada in 2016 (FDA, 2015b; Health Canada, 2016).

### 3.2 Developments in the livestock sector

Within the livestock animal sector, including fish and poultry, biotechnological tools for the development of new breeds have not been employed as frequently as in plants and micro-organisms. However, strategies involving gene editing technologies using site-directed nucleases such as ZFNs, TALENs and CRISPR-Cas have made the specific engineering of food producing animals relatively fast and easy. Within the EU, no genetically modified or gene edited animal has been approved for commercialisation yet. However, worldwide it has been shown experimentally that through transgenesis animals can be generated with new traits that have advantages from a agronomic point-of-view (Tait-Burkard et al., 2018). Using new breeding techniques, such as CRISPR-Cas gene-editing strategies, specific targets can be modified primarily through small insertions or deletions. Animals containing these genetic modifications can be generated in different ways, such as through direct modification of live animals, leading to mosaic organisms, or on the basis of in-vitro produced embryos or modification of donor cells for cloning by nuclear transfer. The latter may lead to homogenously genetically altered animals or to mosaic organisms, depending on the stage of the embryo or cell during modification.

So far, the main traits that have been targeted through recombinant-DNA/transgenesis methods in food producing animals are enhanced growth and disease resistance. However, as of this writing, worldwide only one such modified animal, the abovementioned fast growing AquAdvantage salmon, has been approved for release on the market in a limited number of countries and has not been submitted in the EU for commercialisation. Experimentally many more traits have been targeted, ranging from increased muscle growth (Pursel et al., 1989), enhanced nutritional value (elevating level of for instance omega-3 fatty acids in animal products)(Lai et al., 2006), reduced environmental impact (Golovan et al., 2001), climate adaptation (M.-Y. Chen et al., 2005) as well as enhancing milk yield in cattle, sheep and goats (Houdebine, 2018). Gene edited animals are indistinguishable from animals generated through natural breeding, meaning that at the border this may eventually also result in the import of unauthorised GMOs into the European Union.

At the time of this writing, a single GM animal based on gene-editing has been considered for market release, namely hornless cattle in Brazil with a gene edited Pc *POLLED* genotype. If gene-edited

animals contain edits that do not introduce foreign DNA, such as these hornless cattle, they are regarded as conventional animals in Brazil under Normative Resolution #16 (USDA FAS, 2018). It was, however, reported that the generated hornless animals contained within their genome a duplication of the *POLLED* allele as well as remnants of the repair plasmid (Norris et al., 2019). This transgenic element downstream of the intended *POLLED* allele insertion has the consequence that these animals are GMOs and can no longer be authorized pursuant Normative Resolution #16. Another example of gene-edited livestock are thermotolerant 'SLICK' cattle, also bred in Brazil (Bellini, 2018). These are other likely candidates for commercial release and these may eventually get authorized in accordance with Normative Resolution #16 and enter the supply chain. Other likely candidate GM/gene-edited animals that have been approved or are likely to enter the market are listed in Table 2.

Despite substantial animal biotechnology investments in China, no GM/gene-edited or cloned livestock has been approved for commercialisation. However, several projects on the development of genetically engineered livestock have yielded animals with beneficial traits and are ready for market approval (USDA FAS, 2019).

**Table 2** Examples of genetically modified and gene edited livestock

Modified animal	Modification	Status	Reference
AquaAdvantage salmon (Atlantic salmon)	Integrated construct containing chinook salmon growth hormone gene regulated by ocean pout antifreeze protein promoter sequence	Received market approval in Canada/USA	(AquaBounty Technologies, 2015)
Hornless cattle	Gene-edited <i>POLLED</i> allele, resulting in hornless phenotype	Not approved	(Norris et al., 2019; USDA FAS, 2018)
GM common carp 'crown carp'	Integrated construct containing grass carp growth hormone regulated by common carp beta-actin promoter sequence	Not approved	(Yaping Wang et al., 2001)
PPRSV resistant pig	Gene-edited <i>CD163</i> gene – knock-out of receptor for porcine reproductive and respiratory syndrome virus (PPRSV)	Not approved, research stage	(J. Chen et al., 2019)
SLICK Angus cattle	Gene-edited prolactin receptor gene conferring a thermotolerance 'SLICK' phenotype	Not approved, research stage	(Bellini, 2018; Dikmen et al., 2014)
Beta lactoglobulin free milk cattle	Bi-allelic knock-out of <i>BLG</i> (beta lactoglobulin) gene by ZFN mRNA for the production of hypoallergenic 'designer milk'	Not approved, research stage	(Sun et al., 2018)
ALV resistant chicken	CRISPR/cas9-mediated gene-editing in <i>chNHE1</i> , resulting in $\Delta W38$ mutation conferring resistance to avian leukosis virus subgroup J (ALV-J) infection	Not approved, research stage	(Koslová et al., 2020)
GalSafe Pig	Integrated pPL657 rDNA construct in <i>GGTA1</i> gene, knocking out galactosyltransferase alpha 1,3; resulting in elimination of galactose-alpha1,3-galactose sugar on pigs cells	Received market approval for food and biomedical use in USA	(FDA, 2020; Revivicor, 2020)

### Developments (Expert interviews)

As most important developments in the animal sector, the experts name large-scale breeding programs (see Annex 3, interviews Animal Interviews). The opportunities for genomic prediction and genomic selection and quantitative genetics, based on 'big data' on animal genetics, are expanding. One expert mentioned the increase in large-scale production with more precise techniques.

Some other developments that were mentioned were developments in sperm sorting, and working with embryo's.

The experts did not name gene editing as a prominent development in the sector, despite the examples of hornless cows from Brazil or research into disease resistance. Within the development of vaccines, both for viral and bacterial diseases, there are a lot of examples of the use of NBTs. Gene

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editing for experimental research is prominent. Some experts see possibilities to use editing to study function of genes; knowledge that may subsequently be applied in breeding programs.

When asked for most beneficial developments, experts are hesitant to address these. Several examples of developments are mentioned by the experts: improving animal welfare, (no more need for dehorning of cows, or castration of pigs), improving resistance to (viral) diseases, and reducing environmental impact (Enviro-pig). However, it is questioned if this can be considered beneficial and if the public will see it that way. The current practices are often the cause of (welfare) issues, and changing current practices may be favorable over adapting (the genetic information of) animals. Overall, animal breeding is perceived negatively, and gene editing even more so.

When asked for developments of concern, one of the experts mentions the concern that a long term risk for gene editing, may be loss of genetic diversity. An example is seen in AquaBounty salmon, may lead to a reduction of breeding of other salmon. Gene banks might be a solution to preserve genetic diversity. The reduction in genetic diversity is also relevant for regular breeding techniques, thus careful monitoring of populations is required to avoid problems with decreased diversity. One of the experts warns that for breeding, the claim that gene editing is under control and is similar to regular breeding (risks and safety) cannot be made yet.

Another development is that animals in large-scale farms receive less individual attention. The public perception of small scale farms is better (even if conditions may be worse). Another expert points out that the profitability of producing animal products is very low, which leads to larger farms. Moreover, the power balance in markets may shift, a few large players might monopolize the market using novel techniques. As an example: globally only two companies are responsible for the majority of chicken breeds that are placed on the market.

When asked when animal (products) with base edits will move to the European market, there is no uniform answer from the experts. One of the experts expects that products for pharma will be introduced relatively soon, more than for conventional livestock farming. Another expert points out that reproduction techniques may be a limiting factor in the marketing of gene edited products. How well techniques work, varies per species: embryo freezing for example works well and is easy for cattle, yet difficult in pigs.

A timeframe mentioned is that within 5-10 years some products will come to the EU market, worldwide probably within 3-5 years. Another expert estimates that it would be about 12 years before an edited animal will be developed (four years for developing a particular edit, four years for implementation, and four years for marketing). The limited knowledge of the animal genome and desired effects makes that this can be a long process.

### 3.3 Traceability issues

In accordance with EU GMO legislation, GM animals as well as products derived from GM animals are required to be traceable at all stages of the production and distribution chain. GM animal products that move to the European market will require an event-specific detection method: producers are obliged to supply this detection method that has to meet specific minimum method performance requirements, as well as positive and negative reference materials. These latter materials will be used in the subsequent European validation of the method by the European Reference Laboratory for GMO methods (EURL), the Joint Research Centre in Ispra, Italy, together with the European Network of GMO Laboratories (ENGL). Once this method has been validated and the GMO event is approved, this method will serve to enforce the European GMO legislation. At the same time, strategies have been developed to identify unauthorised GMOs, which may differ per member state. However, the strategies are all based on screening steps using genetic elements that are generally associated with GMO events, and combinations thereof may indicate the likely presence or absence of unauthorised GMOs in a particular product batch. These strategies have been developed for the screening for unauthorised GM crop plant events, but may likewise be applied to identify unauthorised GM animal breeds.

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With the advent of gene-editing breeding techniques, strategies to detect gene-edited GM animals will also be difficult since gene-edited animals are, as with plants, indistinguishable from their conventionally bred counterparts. Because of this fact, detection methods will not be able to clearly state whether the detected events have been created using gene-editing methods or if they are 'natural'. It is generally acknowledged that, also in the case of animals, it will be challenging ('impossible') for applicants to provide event-specific methods as part of the dossier that will meet the minimum performance requirements in terms of, particularly but not only, specificity. Other breeders may set up breeding schemes, legally or illegally, that may result in the same modifications and enforcement laboratories will not be able to distinguish both events. The re-establishment of the same trait, already present in one species or breed, using CRISPR-Cas procedures may likewise be achieved by random repair of double-strand DNA breaks through non-homologous end-joining (NHEJ) causing small insertions and deletions (indels) and point mutations, but increasingly more directly by more precise transformations using homology-directed repair (HDR) strategies. Also, it may be assumed that specific traits will increasingly be based on different types of modifications in the same gene(s). This will make it more challenging to develop informative screening strategies for specific traits.

Current detection methods will often not distinguish specific traits in animal breeds obtained through NBTs from their conventionally bred counterparts with the same mutations. Therefore it will be difficult to establish whether or not a specific trait is related to the (fraudulent) marketing of unauthorised animal products. The diversity of traits related to breed aspects that are well monitored and registered, such as yield and health characteristics, may be well established, allowing for better assessment of new characteristics in this respect, but this will not be the case for the remainder of the traits that are not closely monitored.

When considering a more product-based strategy, it is clear that it will be impossible to unequivocally identify any new product at the border if solely focusing on non-specific DNA mutations. Detection and identification will only be feasible within the framework of a risk-based approach.

Under both scenario's the developments with relation to the production of specific substances in livestock, that may have pharmaceutical properties, will require strict segregation strategies, to prevent the derived animal products with possibly elevated levels of the respective pharmaceutical compounds to enter the food market. As the production of livestock-based pharmaceuticals will be limited, this may not be an issue in practice, but close monitoring will be required in all cases.

### **Traceability (expert interviews)**

The experts indicate that small mutations can be found easily, this happens already in regular breeding (see Annex 3, interviews Animal Interviews). When detecting SNP's: this is variation that is normally present, thus gene editing cannot be proven with certainty.

What complicates traceability even further is the comparison of a reference genome (for pigs Tabasco pig most used) vs genome of the production animal, they are likely to have many SNPs already. With ongoing developments, more line specific genome sequences will be known, however it is expected that there will be many naturally occurring SNPs, which is intrinsic to animal breeding.

Detection of conventional GMO's is easier as larger DNA pieces can be easier found. Experts indicate that the ethical discussions are more important in case of conventional GMO's.

A barcode system, whereby a DNA sequence is added on purpose to enable identification of gene edited animals, may be technically feasible; although the safety of such a system for the animal has to be proven before it may be used. One of the experts notes that a marker should be close to the edited trait, otherwise it may still be lost. It is questionable whether such barcodes are desirable and acceptable for society.

Traceability of specific traits could be done with documentation, but would require transparency and openness.

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## 3.4 Safety issues

The chances that new animal products obtained by the use of NBTs will have adverse effects should not be exaggerated given that generating an 'unsafe animal' is not easy, especially since introducing genetic modifications with a potential adverse effect might have a similar negative effect on the GM animal. However, new techniques may change or introduce metabolic routes, which may result in the production of novel proteins or secondary metabolites that would justify a pre-market assessment. These novel biomolecules will need to be assessed for their bio-active, potential toxic or allergenic activity. Modifications that involve the introduction of a molecule that has antimicrobial activity or relates to growth enhancing hormones to increase production characteristics, may in this way also be relevant to human health because of its bio-active properties. Furthermore, genetic alterations in animals may have unintended, off-target consequences, such as unregulated gene expression, side effects, mutations that alter essential biological processes, as well as the (increased) production of allergenic biomolecules, which may have a negative impact on animal health and well-being. In this respect, it should be noted that off-target effects are more likely to still be present in the marketed production animals, as animal breeding programmes are longer and provide in practice less options to scan for unintended effects in the animal breed characteristics compared to the crop plant situation. With regard to the safety of the products derived from these genetically altered animals, the health and welfare of the animal as such is considered the most important indicator of the derived products.

When procedures such as cloning technologies and gene-editing are applied to generate desired genetic traits in livestock, these procedures might impact animal health and welfare. These issues, however, might only be present in the founder animals, which may then be used in conventional breeding programmes. These animal welfare issues have been the main reason that animal clones and products derived thereof have not received market approval within the European Union. Occurrence of abnormalities associated with animal cloning technologies are generally significantly lower in subsequent conventional animal breeding programmes. Therefore the likely impact on animal health and welfare after commercialisation, when conventional breeding practices are performed, will be reduced when compared to the experimental stage in which the founders are bred, and will mainly focus on the specific aspects of the newly introduced trait(s). This will, however, depend on the intended effect of the genetic modification and will need to be assessed on a case-by-case basis: animal health and welfare are critical issues in the current pre-market assessment strategy for GM animals in the European Union, should there be any applications in this area, which has so far not been the case.

Another safety aspect relates directly to the fact that it will not be feasible anymore to have 'real' event-specific methods for new NBT-based GMOs. The consequence of the presence of the same gene edit and related traits in authorised GMOs and unauthorised GMOs is that the potential unintended effects may differ. This, while in both cases the toxicological characteristics related to the newly introduced trait, the intended effect, are likely to be the same. This is because two procedures to come to a particular gene edit may differ; in one case the off-target effects may be very limited and well-characterised, while in a second programme there may be considerable off-target effects that may have potential adverse effects for humans, animals or the environment. As stated, this will have an higher impact for the animal production sector than for the (crop) plant sector.

### **Safety Issues (Experts interviews)**

Food safety is currently not part of the development of new livestock species, other aspects are considered, in particular animal health, but also behavior, welfare, and environmental aspects (see Annex 3, interviews Animal Interviews). For product safety, conditions in the stables and at the farm, and at production facilities are more important.

The experts state that edited animals will have to be studied for long periods over time to be able to see what the effects are; both of the on-target as well as of potential off target effects. Any mutation may have consequences for the health and welfare of the animal. One of the experts warns that loss of function mutations can have many trade-offs; only with complete knowledge on DNA level and sufficient understanding of biology and physiology to estimate results of an edit these loss of function mutations will be feasible. The experts also stress the importance of careful consideration of edits and related implications, which are to be evaluated on beforehand.

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Concerns lie primarily with off-target effects, long studies on welfare are promoted. Unintended effects of the on-target modification should also be considered.

When asked what should be basic requirements for safety if a product-based approach should be applied in legislation, answers of the experts differ substantially. Considerations before commencing with gene editing procedures were mentioned, for instance what could be desired effects and what are potential adverse effects of the gene edit. The question who can decide what is desirable is raised in the interviews. Overall, animals should be able to function normally, and should not express any behavioural changes because of the genetic alteration. Comparative analysis was mentioned, which components are different between the current and the old animal derived product. Another mentioned that off-target effects should be considered, so that safety of animals is not compromised. The rules for old breeding technologies should also apply to new techniques.

Finally, there were considerations about what should be considered the product – in this respect animals are quite different from plants. Each animal is unique, and testing all animals is not feasible. Overall, the health of the animals is very important for food safety. There is also a link between animal cloning and gene-editing, as animal cloning procedures may aid in the development of gene-edited animal breeds. As with gene-editing, animal cloning may have implications for animal well-being, safety and traceability.

### 3.5 Safe-by-Design

As a means to prevent or reduce risks, both for consumers as well as production animals, Safe-by-Design principles may be incorporated in the development cycle of novel animal breeds. Safe-by-design aims to instil a safety culture via the application of safety considerations throughout the early stages of design and R&D up until market release of a new product. At every stage of the production cycle assessments are carried out to monitor animal breeding steps performed, identify related hazards, perform further hazard characterisation, where applicable, and possibly initiate mitigation strategies that may include the timely adjustment of the breeding programme. Other possible mitigation strategies that may form part of SBD strategies in animal breeding using NBTs may involve the utilization of more specific nucleases with a reduced, preferably negligible, frequency of off-target consequences. Theoretically, off-target genetic alterations due to the application of NBTs may impair animal health and welfare, as well as having the potential to generate undesired gene products such as allergens. Therefore, it is important to reduce the occurrence of these off-target alterations as much as possible, which will benefit the well-being of both the livestock animal and the consumer.

#### **Safe-by-Design (expert interviews)**

Some experts from livestock industry have heard of the Safe-by-Design concept, although familiarity is because of applications elsewhere, no known application in livestock farming (see Annex 3, interviews Animal Interviews). The concept appeals to the experts.

### 3.6 Economic aspects

Animal agriculture is a highly important sector for the Dutch economy and economic perspectives.

New breeding techniques may increase production characteristics of animal-based food products either when beneficial traits are introduced that directly influence yield (faster growth, increased muscle tissue) or through the introduction of traits that stimulate animal health and welfare (disease resistance/tolerance). Both of these strategies can have a potential beneficial economic advantage both for animal breeders and consumers.

When livestock animals grow faster this cuts down on the time needed for the animal to reach a marketable size, and increased muscle tissue directly increases the yield of meat. Both of these

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examples may also have the added benefit of higher feed conversion efficiency, animals that reach the proper size more quickly may, therefore, need relatively less feed.

Traits that reduce the occurrence of diseases by improving disease resilience may clearly also have economic benefits. Reducing the impact of diseases decreases animal suffering with related adverse effects for the growth characteristics of the animals, will reduce the costs associated with veterinary consultations, treatments and in case of potentially virulent pathogens will prevent the untimely culling of livestock. More efficient and disease-free production of animal products could potentially reduce the costs for end-users, the consumers, once products enter the market.

Current developments in livestock biotechnology indicate that these programmes are mainly carried out in non-EU countries. Within the EU, certain animal biotechnology projects are being carried out for agricultural purposes such as research on African swine fever resistance at the Roslin Institute in the UK. Commercial application of animal biotechnology in the EU is regulated under the same process-based legislation as for GM plants, with an additional focus on animal welfare aspects. However, no GM animal for food use has been commercialized in the EU, and at the time of this writing no applications have been submitted to EFSA for the placing on the market of GM animals.

Similarly, current global segregation between different regulatory strategies for the market approval of products from new breeding techniques will likely result in an increasing number of import issues. The extra hurdles for the import of raw materials will negatively affect the European economy at large. The extent of these effects will require further investigations.

At the same time current developments in animal breeding may likewise also offer new possibilities for the sector. There seems to be global concern over the potential of the new gene editing techniques in food applications. If Dutch/European animal products can show that European companies have animal breeding programmes with built-in well-established risk assessment strategies and clear animal care standards this may further add to quality perception of Dutch/European products. This may benefit the sector, especially in times to come when major genetic modifications may become more standard.

### **Economic aspects (expert interviews)**

One of the interviewees indicates that the theoretical possibilities of gene editing are astronomic: with targeted edits, enormous efficiency gains can be achieved, that could result in significant amounts of profit. The bottleneck is knowledge on genes. Another expert states that edits may have to be done in multiple breeding lines, which limits the profitability (see Annex 3, interviews Animal Interviews).

Gene drives are also mentioned as an opportunity, as they would enable a more rapid way to spread a genetic trait in the population, however, due to possible risks of affecting wild populations application of gene drive technology is currently not feasible.

There could be opportunities, as long as companies respect ethical aspects and the intrinsic values of the animal, for example with health benefits for the animal.

When asked for economic concerns, there may be risks when competitors can use techniques, which may result in better breeds. In particular companies with a world-wide market are at risk for those competitors with access to technologies that are not allowed in the EU. Another concern is that the profit of the novel techniques will only go to a few companies with large financial resources. These may be non-European companies from countries where the use of NBTs is less stringently regulated. These may be non-European companies. One of the company-based interviewees indicate that there are few short term concerns, as the American competitors have to comply with FDA rules, as well as consumer attitudes. On the long term, there are still worries the EU will fall behind. Also the risk of larger companies moving abroad is mentioned by some experts.

Another point made by the experts is that the current European climate is not stimulating for research. There is hardly any fundamental research into gene editing in (livestock) animals, also not within leading research institutes. One of the company experts indicated that their company has research done in the USA, where it is easier.



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Other concerns are related to a reduction in genetic diversity, when edits are only performed in most competitive breeds. Furthermore, there are concerns related to the contrast between technological possibilities and societal trends (more attention for locally produced food and artisanal food). When the technology is used by competitors outside EU, Dutch (and European companies) may lag behind in knowledge.

### 3.7 National / EU / global (regulatory) aspects

Besides the economic aspects, genetic engineering and gene editing also face the challenge of social acceptance of applying these technologies in animals. Since any unintended consequences of these techniques may, theoretically, negatively impact animal health and welfare, public perception of these technologies may not be favourable. Modification of traits with the aim to improve animal welfare, for instance modifications that render livestock animals immune to certain diseases, may get more widely accepted by the public (Eriksson et al., 2018; L.J. Frewer et al., 2013).

It is important to note that GM animals can either be generated by engineering of in vitro produced embryos or donor cells for cloning by nuclear transfer. Animal cloning for farming purposes, however, is currently restricted in the EU and there is a ban on food from animal clones as well as from progeny of such clones. In practice, animal cloning may be utilized for the generation of the 1st generation of animals with the desired trait, this first generation will then be bred to produce herds of GM progeny which will need to conform to EU legislation for market approval. Contrary to food producing animals, there is no EU legislation regarding the cloning of animals for non-food purposes, such as for sports and leisure. Whether these cloning practices are allowed is left for competent authorities of each member state to decide. For instance, in the Netherlands animal cloning is prohibited without prior authorization (for instance when used in biomedical research), pursuant to the Dutch animal law (Wet Dieren).

Different considerations apply when considering current developments at the national, the EU or the global level. National considerations relate to the importance of the sector for the Dutch industry, and may relate to specific concerns in some cases with relation to the Dutch environment. For the European context similar considerations may apply on a European level, here also considerations of food or feed safety may be relevant in exceptional cases.

In both cases these aspects are directly related to the potential to be able to identify GMOs at the border. So far, all EU member states have monitoring programmes to analyse food, feed, and seeds (not including animal reproductive materials so far) for the presence of authorised GMOs and, in most countries to a limited extent, for the potential presence of unauthorised GMOs. These programmes, if continued in their present forms, will not be effective to identify the new generation of gene-edited GMOs. As it will be difficult to develop equally effective monitoring programmes for all categories of GMOs in the near future, it seems necessary to consider alternative options in this respect.

On a global level, the main overall interest seems to be to harmonise risk assessment strategies as much as possible in a way that will best guarantee the welfare of our livestock and the safety of related innovative animal products for humans, animals and the environment, without stifling innovation by overly burdensome regulatory requirements. One option in this respect may be to link up to already globally harmonised frameworks, such as principles and guidelines as formulated by United Nations Food and Agriculture Organisation (FAO), or by the World Organisation for Animal Health (OIE), where the latter could cover aspects of both food and feed, but also animal well-being.

When considering a more product-based approach, it is clear, that it will not be possible to assess all products from new animal breeds at the border. It seems more realistic to assume that the situation will become more in line with the approval system of novel foods in Europe, and elsewhere.

#### **Regulatory aspects (expert interviews)**

The main concern when asked for regulatory aspects was similar as for economic concerns, being the lack of opportunities to do research with the new techniques (see Annex 3, interviews Animal Interviews). Without research, no knowledge can be developed in Europe. One of the experts

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illustrates the importance of gaining experience with a new technique, genomics, which is now very important in the livestock sector, is a technique that has been developed over a 25 year-long period.

Although all the experts underline the importance of a harmonisation of regulations regarding NBTs, there is little faith that this is feasible.

The risk of that activities with NBTs are outsourced to countries where regulations are less stringent, is very real. Trade treaties will be a problem, Europe may choose to ban products from other regions. Harmonisation with countries such as Australia and New Zealand is advocated.

One of the experts stresses that gene editing has many different forms (SDN1, 2, 3) – an overarching regulation is not feasible, there should be some distinction between various forms.

## 3.8 Social acceptance and public opinion

Application of animal biotechnology, as aforementioned, may cause unintended adverse welfare problems for the livestock animal. Welfare problems similar to those observed in cloning or genetic engineering practices may also be found in conventional technologies, such as artificial insemination or in-vitro produced embryos, albeit to a lesser extent. However, the impact on animal health and welfare caused by NBTs may further raise ethical considerations and drive social acceptance of the application of the NBTs in animals altogether. It is generally accepted that there are limits to the amount of stress and pain that are ethically justifiable when imposed on livestock animals. In recent years there is a trend that consumers demand better conditions for animals in terms of housing, transport and culling, but are also increasingly prepared to pay premium prices to achieve these improvements (Cornish et al., 2019).

Application of animal biotechnology, and the difficulty to predict related physiological effects in the resulting animals, may lead to levels of pain or stress that exceed these limits and therefore these technologies may not be readily accepted by the public, especially when genetic alterations are introduced in livestock mainly to benefit commercial interests. Further considerations that may influence public opinion are the unnaturalness of genetic alterations and the impact on the integrity of the livestock animals' life (McConnachie et al., 2019). It is important to note that when it comes to the improvement of animal health as well as human public health, then public opinion may be different. For instance, genetic alterations that will benefit livestock health and welfare, such as disease resistance against avian influenza or African swine fever, might be more socially acceptable compared to alterations that solely increase production yield (Eriksson et al., 2018; L.J. Frewer et al., 2013; McConnachie et al., 2019). Public opinion towards traits that confer disease resistance may be more favourable since they might prevent animal suffering caused by disease.

Potential unwanted effects of animal biotechnology resulting in adverse animal health and welfare problems warrant a responsible research and innovation (RRI) approach for this field of biological research. RRI is a broad framework that considers the potential impact of research and development on the society at large with the aim to generate more value for users and society. These RRI goals can be achieved through actions such as stakeholder involvement and the promotion of access to scientific data.

### **Social acceptance and public opinion (Expert interviews)**

Experts from companies are asked how consumers' opinion and public perception affect the work with GMOs, and all indicate that the views of the consumer are very important (see Annex 3, interviews Animal Interviews). The importance of involving the consumer in dialogue early on is stressed by the experts. The large retail players and lobby groups have a big influence, even if a product is safe, the desirability by the consumers determine what happens in the animal production chain. In addition, companies and institutions determine whether the consumer accepts certain technological possibilities, more than the application itself.

Overall, health and welfare promoting edits are considered most likely to be developed and accepted (more than production increasing edits).

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## 4 Sector specific document: Micro-organisms

In this section, the term 'micro-organisms' relates to archaea, bacteria, microalgae, yeasts and filamentous fungi.

### 4.1 Developments in microbial biotechnology

Genetic modification (GM) of micro-organisms important for the food and feed industry has relied in the past on the use of traditional genetic modification methods. However, these traditional GM methods have several limitations such as the requirement of non-homologous end-joining (NHEJ) pathway deficient strains to increase the success of homologous recombination and the need for the integration and presence of a selectable (antibiotic resistance) marker in the genome order to identify positive modified cells. As a result, these methods have been optimized for only a selection of model and industrial microbial strains, in particular for the eukaryotic micro-organisms such as fungi and algae. New genetic modification techniques (NGMTs), or also referred to in this document as new breeding techniques (NBTs) for plants and livestock animals, hold promising applications for the food/feed industry to generate with greater ease and speed improved microbial strains. NGMTs hold new possibilities for GM of micro-organisms, such as marker-free genome editing (Soreanu et al., 2018), multiplex genome editing targeting (Adiego-Pérez et al., 2019) and even the possibility to redesign microbial strains (e.g. the construction of synthetic orthogonal microbial chassis organisms) if gene editing and synthetic biology tools are combined (Chi et al., 2019).

NGMTs have the potential to be of importance for biotechnology food and feed applications involving micro-organisms, such as the ability to edit both existing (e.g. bacteria and fungi) and new cell factories (e.g. algae) for the production of food and feed enzymes, ingredients and processing aids. NGMTs will not only be useful for these compound production applications, but can also be used for modifying the genome of traditional microbial strains (e.g. lactic acid bacteria or beer and wine yeasts) of which food or feed products are made with or produced with. Of all reported genome edited micro-organisms so far that could have a potential use in the food/feed industry, most of them harbour modifications obtained by SDN-1 and in only two examples the modification was obtained by SDN-2 or SDN-3 (Table 3). The white button mushroom is the one of the two gene-edited micro-organisms that has received regulatory clearance in the US. This mushroom was obtained by SDN-1 and only harbours an indel in a gene, preventing the mushrooms to turn brown with the aim to increase their shelf-life and reduce food waste. This gene edited mushroom, however, is not yet available on the market. Gene editing of beer and wine yeasts offers a potential for improving yeast characteristics beneficial for, for example, the fermentation process (e.g. ethanol tolerance) or the final product (e.g. the sensory quality of beer or wine). Research groups in Belgium, Brazil and the US have been using the CRISPR-Cas9 system to genetically modify yeasts (*Saccharomyces cerevisiae*) in order to modify the flavour profile of beer, either reducing the off-flavours or enabling or enhancing (novel) flavour and aroma production (Carvalho et al., 2017; Denby et al., 2018; Mertens et al., 2019). One of the yeasts contains two transgenes that are plant metabolic pathway genes in order to produce aromatic molecules similar to those found in hops, offering a more sustainable beer brewing method as there is no need to add the hops (Denby et al., 2018). This *S. cerevisiae* strain is the only known gene-edited micro-organism so far on the market, sold as a starter culture (named High Sierra or yBBS002) by Berkeley Yeast (formerly Berkeley Brewing Science (BBS)), a startup set-up by the researchers that created this strain (<https://berkeleyyeast.com/beerstrains>). This strain has already been used by multiple microbreweries (e.g. Drake's Brewery Co. and the Fieldwork Brewing Co.) across the US to make craft beers and they are currently being sold locally. Recently, the GRAS application from this company for use of this strain as a starter culture in brewing beer (GRN No. 798) received the FDA's response letter stating there are no further questions regarding that the strain is GRAS under its intended conditions. Berkeley Yeast has currently 7 more so called 'genetically engineered' *S. cerevisiae* strains for both beer and wine-making available on their website of which

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there is no detailed information available about the introduced genetic alterations. Furthermore, Berkeley Yeast offers breweries the choice to develop custom gene-edited yeast strains flavour tailored to specific preferences.

### **Developments (Expert interviews)**

Overall, most important development in microbiology is the development of CRISPR-Cas technology (see Annex 3, interviews Microbiology Interviews). With this new technology, new products/organisms can be developed much faster: what took multiple years in the past can now be done in a few months. The possibility to 'multiplex', or build multiple genes into one micro-organisms is also important. Moreover, CRISPR-Cas makes modifying fungi much easier. Some experts mention the accuracy of CRISPR-Cas, the amount of control over modifications, and the very low occurrence of off target effects, as reasons why CRISPR-Cas is such a promising new tool. Another important development that is mentioned is upcoming use of sequencing techniques (Nano-pore, Pacbio), which lead to knowledge of the genome and thus increased control over micro-organism produced. In addition, robotization is considered an important development, as this increases the speed of strain development. One of the experts states that the focus is now particularly on non-GMO applications, to avoid the GMO regulations.

Even though the majority of the experts considers gene editing and CRISPR-Cas as most important, the developments in sequencing were more often judged as most beneficial. These sequencing data can also be used to select the most promising non-GMO organisms. The strict GMO regulations and (in case of applications for fungi) the lack of experience with the technique are reasons why gene editing is not considered most beneficial.

When asked for developments of concern, most experts mention the public perception towards GMO and gene editing. The distrust towards these techniques from the consumers is mentioned, as is the strong polarisation in discussions, where emotion and scientific (risk-based) arguments are often against each other. Also the focus of consumers on 'natural' and 'biological' food is considered a worrisome development. The experts express their concern that society may miss out on positive contributions that CRISPR may have, for example on sustainability (development of meat replacers) and food security (more resistant crops). In addition, the hinderance of innovation in EU, particular compared to worldwide, is mentioned. The competitive position of European companies compared to China, the United states, and other parts of the world. One of the experts highlights that there are applications of gene editing techniques that are of concern, for example applications in humans, and stresses that ethical discussion and safety evaluations should be held worldwide.

No expert expects unsafe products due to the new techniques.

### **Timeline for moving to the market (expert interviews)**

The experts stress that medicines made with GMO and gene-edited organisms are already on the market, and so are non-food products and cosmetics (see Annex 3, interviews Microbiology Interviews). Also GMO-derived products such as additives, flavours, are already on the market. Some experts expect that there are already products on the market outside of the EU that are made with, but do not contain, gene edited organisms (contained use). Fermented (soy-based) products such as ketchup, is an example hereof. A point of concern mentioned is that large companies will be able to afford the safety dossiers and small companies not.

One of the experts says it will depend on the market and acceptance, to what extend edited products will reach the market. When (certain) food (products) is /are scarce, public acceptance will follow.

Most experts expect that synthetic biology products, with characteristics unknown to nature will not reach the market soon. One expert indicates it will be at least 15 years before synthetic biology products reach the market, this view based on an EFSA report.

**Table 3** Gene edited micro-organisms that have already received market approval and optimised GE microbial industrial strains described in literature that may have a potential use in the food/feed industry in the near future. Note, in this document, the term 'micro-organisms' relates to archaea, bacteria, algae, yeasts and filamentous fungi.

Species	Type of micro-organism	Modification	Gene editing tool	Status	Reference
Agaricus bisporus (White button mushroom)	filamentous fungus	SDN-1 Target: the polyphenol oxidase gene (PPO) Result: reduces browning and increases the shelf life of mushrooms	CRISPR-Cas9	received market approval by the USDA in the US in 2016, but is not commercialised yet.	(Waltz, 2016)
Saccharomyces cerevisiae	yeast	SDN-1 Targets: the FAS2 gene, encoding a subunit of the fatty acid synthetase complex and the TOR1 gene involved in nitrogen-regulated processes Result: higher 2-phenylethyl acetate production capacity, that give rise to the honey-, rose-like flavours in beer	CRISPR-Cas9	fundamental research phase	(Carvalho et al., 2017)
Saccharomyces cerevisiae	yeast	SDN-3 Introduction: two mint and basil terpene synthase genes, the M. citrata LIS gene and O. basilicum ObGES gene Result: the biosynthesis of monoterpenes that give rise to hoppy flavor in beer	CRISPR-Cas9	This strain, and four other genetically engineered strains', are available on the market and sold as a starter culture by Berkeley Brewing Science. Regulatory clearance: GRAS notice on the FDA website. Craft beers using this gene edited strain are sold by microbreweries across the US	(Denby et al., 2018)
Saccharomyces cerevisiae	yeast	SDN-1 Target: the ferulic acid decarboxylase gene (FDC1) Result: reduction of the phenolic off-flavors in lager beer	CRISPR-Cas9	fundamental research phase	(Mertens et al., 2019)
Saccharomyces cerevisiae	yeast	SDN-2 Target: the CAN1 gene of two commercial wine yeasts Result: reduced urea production, the main precursor of ethyl carbamate	CRISPR-Cas9	fundamental research phase	(Vigentini et al., 2017)
Corynebacterium glutamicum	bacterium	SDN-1 Target: the pyruvate kinase encoding gene (pyk) and the lactate dehydrogenase encoding gene (ldhA) Result: improved glutamate production	CRISPR-Cas9	fundamental research phase	(Yu Wang et al., 2018)

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## 4.2 Traceability issues

Within the EU, it will be either challenging or impossible to detect food/feed products accidentally or deliberately containing unauthorized gene edited strains, unless reliable DNA sequence information on the modification is available or may be deduced, as no PCR-based detection method may be (readily) available or lack of information concerning the DNA edit(s) applied in the genome. WGS can be used to detect and/or identify transgenic sequences, gene insertions or gene deletions in these unauthorized microbial strains if compared to a reference strain, but the WGS-approach will be futile to track down small genomic modifications as the genetic changes are undistinguishable from those that naturally.

These unauthorized microbial strains that may accidentally occur in food/feed products or may be deliberately brought on the market may require further scrutiny as to the possibilities to develop effective screening strategies to assess products for their potential presence. In addition, when considering a more product-based strategy, it is clear that it will be impossible to identify any new GM product at the border without prior knowledge of specific small genomic modifications. Even then, it will often be difficult to unequivocally establish the 'gene-edited' nature of a given product such that it would hold in court. Thus, in practice, detection and identification will only be feasible within a risk-based approach, selecting the sequence and related traits that will be given priority in product screening strategies.

### **Traceability issues (expert interviews)**

Experts state that small edits can be detected, by whole genome sequencing or sequencing of particular locations in the genome (see Annex 3, interviews Microbiology Interviews). However, it is not possible to state with certainty whether these result from NBTs or from spontaneous mutations.

Traceability is only possible when companies publish their breeding history. However, also fraud is possible here: it is possible to make it look like a CRISPR-Cas mutant was the result from traditional breeding.

Building in detectable, synthetic sequences, 'barcodes', to mark edited products is possible. However, the experts strongly question whether this would be desirable, as it leads to addition of sequences.

When asked for traceability of specific traits, experts indicate that certain traits can be shown, antibiotic resistance and antimicrobial production could be shown in living biomass for example. Also specific genes can be detected by sequencing or PCR. Proteomics and metabolomics could be used to profile what is changed in an organism.

## 4.3 Safety issues

Products consisting of, containing, or made with GMMs require the assessment of toxins, allergens or other harmful compounds before entering the EU market. The current EU directive for GMMs and the associated risk and safety assessments will possibly be applied to gene edited micro-organisms as well, depending on the outcome of the current legal assessment by the European Commission.

With the use of NGMTs, scientists are able to apply small genetic mutations, insert whole new metabolic pathways or could even create new microbial species. However, there is no reason to assume that gene-edited micro-organisms will not have comparable safety characteristics as the current generation of food-related micro-organisms when considering aspects related to human or animal health. Intended small modifications (i.e. the SDN-1 type modifications) may be comparable types of genetic changes to those that occur spontaneously in nature or via UV/radiation induced traditional methods and thus the safety issues for human and animal health will in theory be comparable. However, it has been shown in a number of peer-reviewed papers in mammalian and plant research that these new gene editing technologies, namely the CRISPR-Cas system, can cause unintended on-target and off-target effects. These unintended DNA changes could, in theory, lead to

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unwanted effects such as the production of unexpected metabolites or proteins that may be toxic or allergenic for humans or animals. However, as the prevalence of unintended effects is low, the risk of leading it to adverse effects is negligible if the frequency is compared to the spontaneous mutations that occur during, for example, cell culturing. If genome editing techniques have been carefully conducted, these off-target modifications will be less abundant than spontaneous and chemical/radiation induced mutations. Combining the relatively new high-fidelity enzymes with optimally designed guide RNAs will further reduce the frequency of off-target modifications the following years.

NGMTs enables researchers to easily improve microbial species or strains for synthetic biology (i.e. development of chassis micro-organisms) and industrial biotechnology. These techniques offer the ability to radically recode the genome of micro-organisms creating man-made species. For example, in a recent study, researchers edited the yeast *Saccharomyces cerevisiae* with the CRISPR-Cas system so that its whole coding genome was placed on one 'super-chromosome' (Shao et al., 2018). Thus, by use of NGMTs, new microbial strains can be created with a spectrum of safety risks for animal and human health, ranging from potential low-risk to high risk strains. As the safety of these recoded organisms has not been assessed yet, these new developments will pose new challenges in predicting and evaluating risks.

The abovementioned examples illustrate that not all micro-organisms genetically modified with the use of gene editing tools will have a similar level of risk and thus potential safety risks for human or animal health have to be evaluated using a case-by-case product-based manner instead of using a process-based approach, focusing mainly on the changes established in the strain.

### **Safety issues (Expert interviews)**

Genome-editing is considered equally safe as traditional mutagenesis techniques, which have a history of safe use (see Annex 3, interviews Microbiology Interviews). The experts state that whole genome sequences should be studied, so that both intended and unintended effects can be checked.

Organisms should be studied within the context in which they are used, for example if there is a chance that the mutation has ecological consequences (which is more likely for plants). The risk of transferring DNA towards other organisms is not a concern, although the application of a modified organisms should be taken into account. Toxicity and toxic by-products are mentioned as important safety risks, that should be checked carefully. In addition, it is stressed that traditional breeding may lead to large genetic changes and this is under the current GMO regulation due to exemption that are not checked.

When asked for the requirements of safety assessment, the experts state that safety assessment should not depend on the technology used to obtain the product, but on the characteristics of the products. The experts indicate that the properties and safety of the micro-organisms (virulence, infectivity, allergenicity, safe history of use) should be considered. In practice, QPS organisms are currently already treated differently than non-QPS organisms. Also the presence of viable micro-organisms in the end product is important. The absence of antibiotic resistance markers should be given.

Some experts state that genomic information should be given, that clarifies the modification made. All modification(s) should be specified, both intended and unintended modifications. There can be unexpected effects, even if the gene modification is (only) in the intended gene; the example to illustrate this was the effect of a gene encoding a cell-wall degrading glucosidase that could (unintendedly) lead to different cell wall composition in an edible mushroom-forming fungus. Defined products should be given.

Other requirements that are mentioned are the assessment of the production methods (for example, heavy metals may accumulate, which would require monitoring.) Moreover, one of the experts stated that for fungi, the scientific knowledge is currently limited, so requirements cannot be set yet. Also the principle of equivalence was mentioned, in particular for lactic acid bacteria and bakers' yeast. The genomes of these organisms have been altered by mankind both intentionally and unintentionally, for a very long time; in a product-based regulation, similar adjustments can be assessed in a similar way.

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One of the experts states that selfcloning should be free from regulations, while for added heterologous sequences a product-based approach should be applicable.

The experts from business were asked in what way food safety is already taken into account in the development of new (genetically modified) organisms. One of the business-based experts indicates that the current legislation for safety in GMM legislation is very clear. Safety is taken into account from the start of the process, in a Safe-by-Design manner. Micro-organisms are killed at the end of the production. Marker free strains that do not have antibiotic resistance genes are used. Any risks of toxins can be removed from strains, so rational risks can be reduced.

### **Safe-by-Design (Expert interviews)**

During the interviews, the experts stress that Safe-by-Design is integrated in the way of working in companies (see Annex 3, interviews Microbiology Interviews). In early development stages (labwork), all aspects of a to-be-marketed product are taken into account, of which safety is an important factor. One interviewee mentioned that Safe-by-Design can mean that properties are implemented to ensure that micro-organisms can only survive inside the (specific conditions in the) reactor; but this is not familiar with any examples from practice.

The idea among experts is that with new techniques, in general the safety risks can be reduced. One expert said that modern technology can be used to screen new organisms. For example WGS is used to study the effects on DNA, for example to screen mutants for both targeted and unintended genetic modifications. By use of this pre-screening, unwanted organisms can be removed from the process at an early stage. With these extra controls during the design process, safety risks are even further reduced.

## **4.4 Economic aspects**

### *Gene editing technologies will help to manoeuvre into new areas of microbial biotechnology*

The current regulatory requirements and safety assessment of gene edited microbial food/feed products will definitely have an impact on innovation within the EU and could delay the pace of commercialization. For the Netherlands is important to maintain its strong position in microbial industrial biotechnology, especially in the food and beverage sector where food enzymes (used for starch processing and in the dairy industry) and fermentation products (beer) are examples of important exported products. Europe is a major player on the global market for industrial enzymes such as food enzymes. NGMTs can speed up microbial strain development for the food/feed industry and thus construction and application of microbial cell factories for improved production of enzymes. The development of NGMTs for strain development not only serves for increasing the overall production but it makes it possible to modify new species of micro-organisms that could synthesize novel enzymes or compounds with a potential use as food/feed enzymes or additives. New gene editing tools also make it possible to engineer the genome of a wide range of species, such as microalgae, that were relatively difficult to modify using more traditional genetic engineering methods. Microalgae are a promising alternative source of protein and high-value nutrients for both humans and animals. Algal species designed with NGMTs may positively affect the position of Europe in the new areas of food biotechnology.

### *Using waste streams with inactivated GE microbes in our future circular agriculture*

As the EU is moving towards a circular economy, residual biomass waste streams from the biobased industries are a promising feed protein source for livestock. For example, Dried Distillers Grain (DDG) or Dried Distillers Grain with Solubles (DDGS) are waste by-products from the distillery and the bioethanol industries, resulting from the fermentation process of plant-derived sugars into alcoholic beverages or biofuels by genetically modified yeasts (*S. cerevisiae*). In the US, several biomass waste streams with inactivated genetically modified *S. cerevisiae* (IMSC) strains for the use as livestock feed have undergone a GRAS evaluation by the FDA. Several biomass waste stream IMSC strains are now considered safe to use as livestock feed in the US. These *S. cerevisiae* strains are all modified using traditional genetic modification methods. No livestock feed consisting of GM yeast have been authorized to enter the EU market. If the Netherlands and other EU members will move to a circular



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economy, different biomass waste streams could be considered for recycling as feed materials, including lignocellulosic waste streams containing inactivated GMMs from the biobased industries. It is expected that the biobased industries worldwide, will eventually move to the NGMTs to modify their strains, as it is faster, cheaper and easier than the traditional methods. As for the EU, there are novel safety, traceability and economic issues (e.g. the lack of detection methods) to consider in this area and with these novel GE tools, the GMM safety assessments for livestock feed have to be adjusted accordingly.

#### **Economic aspects (Expert interviews)**

In some interviews, the economic consequences were discussed (see Annex 3, interviews Microbiology Interviews). There was worry that current GMO legislation will be in place for years, negatively affecting the innovative strength of European sector.

The targeted mutagenesis can prevent the occurrence of additional mutations affecting the fitness of a production organism, that occur with classic mutagenesis. With a product-based legislation, it is likely that products with genome editing are more easily approved, hence supporting innovation.

## **4.5 National / EU / global (regulatory) aspects**

In the EU, all foods and feeds consisting of, containing or produced from GMOs, or containing ingredients produced from GMOs fall under regulation (EC) 1829/2003. GMOs obtained through mutagenesis are exempted; they can be marketed without risk assessment, traceability or labelling (Directive 2001/18/EC). The EU makes a distinction between the contained use of GMMs and the environmental release of GMOs (covering also other kingdoms beyond micro-organisms). These uses are regulated by Directive 2009/41/EC and Directive 2001/18/EC, respectively, both providing very similar definitions of techniques of genetic modification. Within the meaning of the latter directive, the Court of Justice of the EU, however, decided that, in general, organisms obtained by NGMTs are GMOs. It remains unclear to which extent the Court's decision applies to GMMs obtained by new techniques of directed mutagenesis as well, this is currently being assessed by the legal department of the European Commission.

In the US, micro-organisms with edited genomes that contain no foreign DNA are currently not legally viewed as 'genetically engineered' yet still may have to conform with more broadly scoped safety requirements, such as in the case of microbial pesticides, foods, drugs, etcetera. Even if no regulation specifically applies, intergeneric microorganisms, including those that have undergone mutations, for example, still have to be notified to the Environmental Protection Agency (EPA) via a Microbial Commercial Activity Notice under the Toxic Substances and Chemicals Act. The EPA will then assess if the microorganism and its manufacturing process may pose unreasonable hazards to human health and the environment (Wozniak et al., 2013).

Different considerations apply when considering current developments at the national, the EU or the global level. National considerations relate to the importance of the sector for the Dutch industry, and may relate to specific concerns in some cases with relation to the Dutch environment. For the European context similar considerations may apply on a European level, here also considerations of food or feed safety may be relevant in exceptional cases.

In both cases these aspects are directly related to the potential to be able to identify GMOs at the border. So far, all EU member states have monitoring programmes to analyse food and feed for the presence of authorised GMOs and, in most countries to a limited extent, for the potential presence of unauthorised GMOs. These programmes, if continued in their present forms, will not be effective to identify the new generation of GMOs. As it will be difficult to develop equally effective monitoring programmes for all categories of GMOs in the near future, it seems necessary to consider alternative options in this respect.

On a global level, the main overall interest seems to be to harmonise risk assessment strategies as much as possible in a way that will best guarantee the safety of innovative products containing or

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derived from gene edited micro-organisms for humans, animals and the environment, without stifling innovation by overly burdensome regulatory requirements.

When considering a more product-based approach, it is clear, with the speed of innovations in this sector as provided in Table 3, that it will not be possible to assess all products from new microorganisms at the border. It seems more realistic to assume that the situation will become more in line with the approval system of novel foods in Europe, and elsewhere.

### **Regulatory aspects (Expert interviews)**

During the interviews, it is stated that current legislation is hindering the application of NBTs in microbiology, and the drafting and approval of new legislation is a concern (see Annex 3, interviews Microbiology Interviews). International harmonisation would be favourable for internationally operating companies. If an important market differs and has more stringent rules, these are applied to other regions. Only if the market is very large, diversification in development trajectories would be feasible. One of the interviewees explicitly states that current legislation withholds companies to use NBTs for commercial purposes, and makes that traditional mutagenesis methods are applied, that are slower and less precise.

Legislation should be based on scientific arguments, and should be proportional and predictable. It is incompatible that products obtained with traditional mutagenesis are intrinsically safe, while products with modern mutagenesis require additional safety assessments. If regulations for the 'Workhorses of the industry' could be dealt with first, this would greatly simplify matters.

Some interviewees indicate that worldwide harmonisation is the most favourable condition, but expect that this would be a too lengthy trajectory. Others indicate that Europe's legislation is most aberrant, and that altering European legislation would be most practical solution for international harmonisation.

One of the experts sees a possibility for Europe to fulfil a pioneering role in the world, so other regions may follow (South America, Asia). This does require harmonisation within Europe first, which is not yet a done deal.

Finally, small companies indicate their disadvantage in the complex regulatory framework, as large companies are better aware of details in regulation. Platforms might help smaller companies to discuss regulations.

## **4.6 Social acceptance and public opinion**

Social acceptance and the public opinion about GMOs could be one of the factors in determining whether the development of NGMTs will expand or stagnate. Since the commercialization of GMOs, surveys monitoring the consumer attitudes towards them have gained insight into the acceptance of GMOs by the public. The benefits and usefulness of the product can be associated with GMOs, such as being healthier, animal friendly or having cost advantages may play an important role in the overall acceptance. It is known that GMOs have different levels of acceptability; some types of GMOs will be more accepted by the public than others. As described in the general introduction, research showed that genetic modification is supported among consumers to a much greater extent for use in crops rather than for use in animals. GMOs not directly used in food products, but used as production hosts for a variety of food or feed ingredients, are more accepted by consumers. An example is 'vegetarian' cheese made with microbial processing aids (i.e. bovine chymosin from GMMs), produced by industrial transgenic micro-organisms such as *Escherichia coli* K12, *Kluyveromyces lactis*, *Aspergillus niger var awamori* (Kumar *et al.*, 2010). GM chymosin has been used since the 90s and most of the cheese in the UK is made with microbial rennet. This food products has been accepted by consumers and this may be explained by the fact that: a) cheese made with processing aids produced by GMMs does not require labelling so the public is unaware or b) the product itself does not contain a GMO, but is made with a processing aid or contains an ingredient produced by a GMO. As a consequence, it is expected that gene-edited micro-organisms will be mostly industrial strains producing food processing aids and

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ingredients, these types of GMOs may receive a higher level of acceptance by the public than the gene-edited micro-organisms that are part of the food or feed product.

### **Social acceptance and public opinion (Expert interviews)**

Public and consumer perception of modified food is an important topic (see Annex 3, interviews Microbiology Interviews). Interviewees indicate that ethical aspects should be covered. The focus of consumers on 'natural' and 'artisanal' ('ambachtelijk' in Dutch) is mentioned frequently, and is indicated as a worrisome development by some interviewees, as this is an emotional factor. In debates, emotion and scientific-based facts get mixed, leading to unbalanced (unproductive) discussions. In the emotional debate, rational risk analysis is not possible. Technological agreements can be reached with the authorities, but public is major stakeholder that prevents that such agreements are reached.

The opportunity of NBTs to contribute to more sustainability is mentioned. There are worries that the opportunities will be missed by emotional arguments in GMO debate

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## 5 Report series online workshops

A series of online workshops with the title 'Towards new legislation for modern biotechnology in the EU: Opportunity or burden?' was held in October 2020. There were three sessions, focussing on the Dutch plant breeding sector, the Dutch industrial microbiology sector and Dutch livestock farming.

### Program of the workshops

The program for the workshop was as follows (in hours since start)

0:00-0:10	Welcome & Introduction
0:10-0:30	Presentation: Various editing techniques, (GMO) legislation, enforcement issues
0:30-0:40	Plenary explanation of possible legislative scenario's
0:40-1:45	Discussions in smaller groups
1:45-2:00	{Break}
2:00-2:30	Plenary discussion of outcomes & closure

The presentations of the different workshops were similar, although tailored to the specific sector.

### Setup of the discussion groups

The participants were asked to join a subgroup in Microsoft Teams, moderated by two hosts of the project team (one chairing, one taking notes). Each participant was asked to introduced themselves briefly. Next, the participants were asked one by one to rank the presented scenario's (listed below) according to their personal preference, and to present arguments supporting this ranking. Participants discussed the scenarios amongst themselves, whilst the hosts asked additional questions (clarifying, deepening or broadening), when necessary.

In addition, the following questions and statements were used to steer the discussion (when necessary):

- If you were free to add or alter a legislative scenario, what would you change?
- Within the chosen scenario, food safety & public health continue to be safeguarded equally well as under current legislation
- Off-target effects of gene editing techniques are sufficiently covered in the chosen scenario
- "Europe is at risk of falling behind, because the use of new techniques is being held back by the strict GMO regulations"

### The scenario's that were used for the input of the subgroup discussions

#### 1. Current EU situation

In this scenario, current EU GMO regulations are retained. All gene edited organisms (SDN-1, SDN-2, and SDN-3 edits) are regulated as GMOs and will require pre-market approval according to Directive 2001/18/EC for the deliberate release of GMOs into the environment, such as for cultivation, for placing on the market as foods and feeds (Regulation (EC) 1829/2003), labelling and traceability (Regulation (EC) 1830/2003), and contained use in case of genetically modified microorganisms (Directive 2009/41/EC).

#### 2. Small edit exemptions

Similar to current situation as described in 1), however small gene edits are exempt from regulation. These exempted are SDN-1 edits (resulting from DNA repair following non-homologous end-joining) and SDN-2 edits (resulting from DNA repair with a template for the desired genetic alteration. They are treated the same way as random mutagenesis techniques (by means of ionizing radiation or use of mutagenic chemicals). Products with SDN-3 edits require approval.

#### 3. Product-based approach

GMOs as well as any other organisms may have to be assessed for their safety, on a case-by-case, depending on their novelty and risk characteristics. Only novel organisms and novel genetic alterations require regulatory approval, which would also include novel edits (be it SDN-1, 2 or 3).

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Product developers will be able to consult with authorities whether their product is novel or not. Depending on the outcome, a safety evaluation dossier for the novel product may have to be submitted to authorities. Similar scenarios are currently in place in Canada for novel organisms, foods and feeds.

**4. Altered GMO definition**

In this scenario, an alteration of the legal GMO definition is in place, that excludes certain gene-edited organisms. A changed definition would to exclude organisms that were created without the introduction of foreign DNA (such as vectors, repair template, etc.); SDN-1 type edited organisms that were created without the introduction of DNA constructs (e.g. by temporarily introducing the sgRNA & CRISPR Cas9 ribonucleoprotein complex, or mRNA encoding them) would no longer qualify as GMOs. Applicants may consult with competent authorities whether their product is indeed a GMO.

This scenario is comparable to the legislation currently in place in Australia where “A mutant organism in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species)” is not regarded a GMO (OGTR, 2019).

**5. Altered risk assessment**

In this scenario, the current GMO legislation is retained, although the guidance for risk assessment is altered. This means amending the risk assessment under the current legislation. Owing to higher precision, SDN-1, 2, 3 edited organisms would require less data. Data requirements may be limited, for example, to molecular characterization, bioinformatics and phenotype analysis.

## 5.1 Outcomes workshop Plant breeding

### **Scenario 1 Current EU situation**

The current EU legislation scenario is considered the least popular. When current regulation is retained, the EU will have an exceptional position worldwide; in these terms, the EU will ‘miss the boat’ when it comes to new breeding techniques.

This scenario is not feasible in the long term: breeders may use plants from elsewhere in the world, and there is no way to determine whether these have been edited. On the other hand, there is clarity with this scenario, as clear boundaries are defined for what is a GMO and what not.

### **Scenario 2 Small edit exemptions**

The scenario of exempting small edits (SDN-1 & SDN-2) from regulations is most probable, as it is seen as a fast and feasible solution.

There is a distinction between own and foreign DNA, which is feasible for enforcement (as SDN-1 and SDN-2 mutations may be difficult to distinguish from mutation breeding).

Although this is considered a short-term solution that can be implemented relatively fast, making these small amendments may not yield futureproof legislation. There is a need to look further ahead: participants mention a tiered, multi-stage approach to change legislation and to avoid adding too many exemptions to current regulation.

### **Scenario 3 Product-based approach**

This scenario is one of the least popular, for which the main reasons are the uncertainty regarding the requirements for applications (what is novel?) and the lengthy and costly approval process. Also, crops made with conventional breeding techniques (now exempt) usually have novel traits, and therefore may have to be regulated, depending on the risk characteristics analogous to the Canadian example.

One participant had a preference for a product-based approach and use of the CBD’s definition (which leaves more space).

#### Scenario 4 Altered GMO definition

This scenario was the second most favourite of the plant sector workshop. The feasibility of changing the definition is considered lower than scenario 2.

Using the definition from the Cartagena protocol may be useful, but it is unclear how SDN-2 will fit in. The consumer has a major voice in this scenario.

#### Scenario 5 Altered risk assessment

This scenario was on the third place. Europe may fall behind the rest of the world. In addition, with this scenario it is still difficult to predict when products will be accepted. Also, it is easy to circumvent the legislation, gene edits cannot easily be recognized. Products with edits will still have to be labelled as GMO.

Some arguments in favour of this scenario were the fact that legislation does not have to be adapted, and it could be a practical solution for the current situation.

**Table 4** Rankings scenario's workshop plant breeding

		1. Current EU situation	2. Small edit exemption	3. Product-based	4. GMO definition	5. Risk assessment
Subgroup 1	Participant A	3	1	4	2	5
	Participant B	5	2	3	1	4
	Participant C	5	1	3	4	2
	Participant D	3	1	5	2	4
	Participant E	3	1	5	2	4
Subgroup 2	Participant F	5	3	1	2	4
	Participant G	4	1	5	2	3
	Participant H	5	1	4	2	3
	Participant I	5	1	3	2	4
	Participant J	4	2	5	3	1
	Total score	42	13	38	22	34
	Average score	4.7	1.4	4.2	2.4	3.8

#### Other scenarios

When asked for alternative scenarios, one participant proposed a situation where no GMO legislation at all was in place. Other regulations such as the general food law, which would then still be in place, should guarantee the safety of food.

#### Food safety

With regards to food safety, the question is why there are such stringent regulations for editing techniques. Gene editing is considered safer than random mutagenesis and conventional cross breeding, as there are far fewer off-target modifications. Cross breeding is considered more of a risk, as a new cross is developed, while it is unclear what happens at the DNA level. Nevertheless, the experience with conventional techniques shows that the risk of new toxins is very small.

Regular selection procedures are in place, and potential risks are mitigated using common back-crossing processes. For example, a known issue in potatoes is the presence of solanine. Plant breeders take this into account and measure the presence of solanine during the breeding process.

Finally, a risk-free society is impossible. If all risks have to be mapped, all plant breeding might have to be ceased.

#### Economic consequences

There is discussion about the chance that companies may move away from Europe due to the legislation in the EU. There may be different, parallel breeding programs within large multinational

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companies that could help to cope with this, although the economic feasibility of this approach is questioned.

Finally, a participant notes that gene editing may be overrated, as only a limited number of traits can be made with this technique, and it will not fully replace the conventional breeding techniques.

### **Other discussion points**

Participants point out that, in many discussions, the focus is on the techniques alone, yet the benefits of the new technology and what can be achieved with them, should be taken along (as is done for example with medicines). There are many options of new breeding techniques in contributing to sustainability (such as in the Farm-to-Fork Strategy).

In one group, the consequences of labelling were discussed: the GMO label scares consumers off. Gene editing can also be a useful tool for research: studying functions of genes; without necessarily commercialising edited crops.

The need to educate the consumer was voiced, which will be a difficult task due to the stigma of genetic modification. The sector takes little initiative, this is a clear responsibility of the government. There is a need for clarity, in current as well as future legislation.

Each change in legislation will give rise to a discussion in Europe.

## **5.2 Outcomes workshop industrial microbiology**

### **Scenario 1 Current EU situation**

This scenario is considered least favourite.

The current legislation is considered outdated and leads to a situation where the EU cannot compete with the rest of the world.

The discrepancy between allowing mutations resulting from random mutagenesis compared to the strict regulations for the precise technique of gene editing is considered out of line. Gene editing has to be labelled as genetic modification. In practice, this may mean that gene editing is used in research to study the effect of a certain mutation, while the final product/ organisms is created using random mutagenesis. Another point made is that 2001/18 is mainly focused on plants, not tailored to the industrial microbiology sector.

Scenario 1 is not considered to be fit for future.

### **Scenario 2 Small edit exemptions**

This scenario is ranked third, but only just behind scenario 4.

Scenario 2 is considered a practical solution, as it seems feasible to adopt this scenario within a short time; and working with gene editing techniques would be enabled. One participant worries that this scenario comes down to 'tampering with' the GMO regulation, which may be less favourable (due to public opinion). Another participant expects this scenario would be the clearest, as point mutations, most similar to natural variation, would be exempted from GMO regulation. Organisms containing foreign DNA would be GMOs, although it is as of yet unclear how organisms with multiple (complex) mutations would have to be handled.

**Table 5** *Rankings scenario's workshop industrial microbiology*

		Current EU situation	Small edit exemption	Product-based	GMO definition	Risk assessment
Subgroup 1	Participant A	5	2	1	4	3
	Participant B	5	1	3	2	4
	Participant C	5	3	1	4	2
	Participant D	5	3	2	1	4
	Participant E	5	4	1	2	3
Subgroup 2	Participant F	5	1	3	2	4
	Participant G	4	3	1	2	5
	Participant H	5	2	4	1	3
	Participant I*		1			
	Participant J	5	4	1	3	2
	Totals core	44	23	17	21	30
	Average score*	4.9	2.6	1.9	2.3	3.3

\*One participant felt not in a position to judge all scenario's; the score of this participant is not taken along in the average.

### Scenario 3 Product-based approach

Overall, this scenario is considered most favourable.

It is considered a practical solution for the sector; the case-by-case assessment and the separation of product and process are appreciated. The risk profiles of existing products are known, which enables risk assessments to be tailored to new or modified products (fitting to the high risk product).

The Canadian situation is mentioned, but not considered as the best example: the Canadian legislation is not 100% product-based, and also there is ongoing discussion on the definition.

### Scenario 4 Altered GMO definition

This scenario is ranked second, only just before scenario 2.

The exact formulation of the new definition is important: some worry that only excluding SDN-1 type mutations would still lead to a problematic situation for the sector. It is appreciated that labelling would no longer apply for some gene edits.

One participant worries that the altering of the definition is very complex. In this scenario, there is also a chance that the public considers it as 'tampering with' the GMO regulation (like scenario 4).

### Scenario 5 Altered risk assessment

Overall, this scenario is ranked fourth by the participants. This is mainly due to the unclarity of what the new risk assessment would entail. It is indicated that current dossiers are a heavy burden for the industry, and that the link with safety is not always clear.

### Alternative scenarios

Most participants agree that none of the proposed scenarios is ideal. More details would be required to truly judge the scenarios proposed here. One participant points out that the topic is fairly complex, should be thought through thoroughly, and that any scenario will lead to discussion.

When asked for alternative scenarios, the idea that mutations that could occur naturally should not to be considered genetic modification, was proposed in both discussion groups.

There could be a sharp distinction between homologous DNA (non GMO), and heterologous DNA (GMO, for example SDN-3). Another participant notes that large genetic changes can also occur naturally (see, for example, yeast used for beer production), and that this should be included in the discussion on the safety of new techniques.



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### **Procedures new legislation**

One participant lists the criteria that should be considered when picking a new scenario as follows: it should 1) give space (to use new techniques), 2) not lead to a competitive disadvantage compared to other parts of the world, 3) be science based, and 4) always with 'safety first'. A Risk assessment should always be included, in some way.

The lengthy procedures for adjusting European legislation and its negative consequences are discussed. Finally, the possibility that new legislation may lead to extra regulation of conventional mutagenesis techniques is raised.

### **Food safety**

Overall, gene editing is considered safer than random mutagenesis, as the modification is controlled carefully, and off-target effects are checked. Micro-organisms are sequenced in their entirety. CRISPR Cas is very precise, and the chance of mistakes very small.

There are no examples of GMOs or edits that later turned out to be unsafe. Overall, it is expected that the food safety and public health will remain at the current standard with alterations in legislation.

### **Competitive Position of Europe**

Participants pointed out that the long approval procedures are an important reason that Europe may fall behind.

The benefits of the techniques, for efficient production, novel protein sources, and sustainability should be considered more, thereby Europe opposes its own interests. Innovation is faster in other countries, and there are worries about the enforcement for products from outside the EU (example RASFF on enzyme preparations with antibiotic resistance genes.)

A request for an international level playing field is made, to prevent Europe being less attractive to multinationals. The openness about sequences (Nagoya protocol) may lead to firms avoiding certain countries.

Public discussion on new techniques, with information to the public, is requested by one of the participants.

Finally, it is mentioned that the Netherlands, with its knowledge (i.e from TNO and WUR) may function as a guiding country in this regard.

### **Important issues for industry**

The sector currently struggles most with the (financial) burden of safety dossiers, and the rules on labelling. The novel food procedure is considered very burdensome, as well as the registration of new strains, in particular for the small and medium size companies.

With regards to labelling, labelled products may scare off consumers. Also in case of beneficial mutations (such as deletion of an antibiotic resistance gene), products would still have to be labelled. Labelling of food products leads to compromises in the food chain.

When making new legislation, it is proposed that the position of the industry is considered, and requested that the new rules will not be too complicated. A phased approach is considered: exemptions in the short term, and a more thorough approach for the long term. More room for innovation would be appreciated.

## 5.3 Outcomes livestock sector

In this workshop, most participants were very hesitant to give a ranking. Some only wanted to give a most and least preferred option, whilst some others wished not to rank at all. Therefore, some scenarios are not addressed.

### Scenario 1 Current EU situation

Overall, this scenario was considered by part of the participants as least favourable, as there is very little opportunity to make any use of the techniques.

Another participant, however, was most in favour of this scenario, as it is closest to what the public wants at the moment, with the comment that public engagement is lacking from all scenarios.

### Scenario 2 Small edit exemptions

One participant ranked this as most favorable, as it would enable industry to use at least some gene editing techniques.

### Scenario 3 Product-based approach

The participants were quite divided on the suitability of this legal scenario.

There is uncertainty on how this would work in animal based products (milk, meat): would the product or the animal be judged? In case the animal is deemed the product, ethics and animal wellbeing would be important considerations. A concern for potential high workload for applicants was voiced. If the public favoured this scenario, it could be an option.

### Scenario 4 Altered GMO definition

The concern was raised that changing the GMO definition would be problematic for public opinion.

### Scenario 5 Altered risk assessment

No comments on this scenario were made.

**Table 6** Rankings scenario's workshop livestock animals.

	Current EU situation	Small edit exemption	Product-based	GMO definition	Risk assessment
Participant A	5	1	3	2	4
Participant B*					
Participant C*	5		1		
Participant D*	1				
Participant E*	5		1		
Participant F*			5	1	

\*Most participants wished to give no preference, or only a best- and worst-case ranking; therefore no average scores are given.

### Societal aspects and public engagement in legislation

The concern what would happen to public opinion when altering legislation or adopting new legislation is prominent in the discussion.

Input on how to govern the technology and questions such as 'what do we want as society' are important. There is a willingness to use these tools; but this may come at a cost, and it is important to know when it is allowed. If edits could reduce the risk of zoonoses for instance, then these relevant edits might be more socially accepted. More focus on health, human health and societal benefits may help for acceptance.

In companies there are concerns about a future in which new techniques will be allowed everywhere, except in the EU. There are opportunities for the use of gene editing techniques. Specific uses, such as

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prevention of zoonoses, may get public support. However, it may also be argued that the animal breeding system needs to change, instead of changing the animal by using gene editing methods.

All agree that products should be safe and animal wellbeing should be ensured. Animal health overall is very important, developers need to ensure that edits will not negatively affect animal health and wellbeing. One participant voiced the opinion that the government should forbid patenting of genetic edits, to prevent that farmers only have one single provider.

In the described scenario's, public engagement is lacking; there is no clear description on how to use public engagement for governing the technology. Moreover, the values and purposes behind the legislation are not described in the 5 scenarios.

Despite novel breeding techniques, dynamics such as societal framings and questions may not have changed. If the public cannot influence the debate, there could be a sense of betrayal.

Even if legislation is more favorable towards GMO use, the public may not be so optimistic about GMOs, see Brazil for example.

The idea was mentioned that an inclusive way of dealing with GE/GMO may be an advantage in the long run. In the original GMO debate, the promises were big, but they did not become reality. If GMO and gene editing are not allowed, other technologies may thrive, meaning that the EU is still competitive. A new green EU without GM/GE animals may be a good opportunity.

New legislation for livestock farming: could be an opportunity to have public engagement in legislation.

## 5.4 Familiarity with Safe-by-Design

Finally Safe-by-Design was addressed in the plenary session, and explained using the figure from Van der Berg et al. The concept was known by all participants in the microbiology sector, and they also indicated that their way of working was in line with the concept. In plant science, the concept was familiar to only part of the participants, yet most of them indicated that their way of working matched the described way of working. In the animal sector, the Safe-by-Design concept was least known.

**Table 7** Participants of the three workshops

Workshop	Participant	Organisation	Function
Animal		Topigs Norsvin	
Animal		CRV	
Animal		Hendrix-Genetics	
Animal		WUR	
Animal		COGEM	
Animal		WUR	
Animal		Centre for Genetic Resources	
Micro		The Protein Brewery	
Micro		DSM	
Micro		DuPont	
Micro		DuPont	
Micro		The Protein Brewery	
Micro		DSM	
Micro		Corbion / WUR	
Micro		TU Delft	
Micro		COGEM	
Micro		DDNA-Biotech	
Plant		Rijk zwaan	
Plant		Enza Zaden Seed Operations B.V.	
Plant		Vegetable seeds BASF	
Plant		Solynta	
Plant		Holland Bio	
Plant		Anthura BV	
Plant		Genetwister	
Plant		Plantum	
Plant		Plantum	
Plant		KWS vegetables	
Plant		Dummen orange	
Plant		Floricultura	

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# Annex 1 Expert interviews Questionnaires

## A1.1 Plant Sector

### *General developments in plant breeding*

- What do you consider as the most important developments in plant breeding? Specific examples? *CRISPR-Cas and all related developments*
- What do you see as the most beneficial developments? Specific examples? *Disease resistance?*
- What do you see as developments of concern? Specific examples? *The speed of the developments with no clear focus on safety aspects*
- What do you see as a realistic timeline for
  - CRISPR-Cas / gene edited plant products moving to the European market based on base editing
  - CRISPR-Cas /gene-edited plant products moving to the European market based on HDR procedures
  - Synthetic biology – derived plant products, with characteristics unknown to nature, moving to the European market
- What do you see as major issues when comparing the current basically process-based regulations versus an alternative product-based regulations? *How to identify developments of concern*

### *Traceability issues*

- Do you see possibilities for the development of event-specific methods for new gene-edited crop plant varieties?
- Do you see options for traceability of multi-edited crop plant varieties?
- Do you see possibilities for the traceability of specific traits? If so, what do you see as bottlenecks for adequate tracing of traits of potential concern?
- In your view, what should be the consequence of a possible product-based approach in terms of traceability, in other words, what would still be relevant for monitoring programmes?

### *Safety issues*

- What do you see as the major issue(s) when considering the safety of new gene-edited crop plant varieties?
- When moving from a process-based regulation to a more product-based approach, what should be the basic requirements in terms of safety of new plant products?
- Would your concerns be primarily related to the intended effects or to potential unintended effects?
- When considering multi-edited GMO events, could you think of situations where segregation of the edits in subsequent generations could lead to safety concerns?

### *Economic aspects*

- What are your main concerns in terms of economic effects of the increased application of NBTs? Specific examples?
- What do you see as the main economic opportunities of the application of NBTs? Specific examples?
- What are your main concerns in terms of economic effects of the current (regulatory) situation with relation to the application of NBTs in plant breeding, in a Dutch and/or European perspective?
- Where do you see possibilities to benefit from the current (regulatory) situation with relation to the application of NBTs in plant breeding, in a Dutch and/or European perspective?
- More in general, what are the fields of application of the NBTs that are the most relevant for the Dutch/ European situation? Specific examples? And are there alternative routes to reach the same goals without the use of NBTs? What would be the consequences of the alternative routes?

### *National / EU / global (regulatory) aspects*

- When looking at the international perspective, what are your main concerns related to the upcoming application of NBTs in plant breeding? What do you see as the major issues in this respect? Specific examples?

- Do you believe that harmonisation of regulatory requirements is important in this respect? Specific examples to underpin your conviction?
- What would be your preferred route of harmonising regulatory requirements? Who should take the initiative to come to harmonised requirements? Would you be willing to participate in meetings on harmonisation (should these be organised at some stage)?

## A1.2 Animal Sector

### *General developments in animal breeding*

- What do you consider as the most important developments in animal breeding? Specific examples?
- What do you see as the most beneficial developments? Specific examples?
- What do you see as developments of concern? Specific examples?
- What do you see as a realistic timeline for
  - CRISPR-Cas / gene edited animal products moving to the European market based on base editing
  - CRISPR-Cas /gene-edited animal products moving to the European market based on HDR procedures
  - Synthetic biology – derived animal products, with characteristics unknown to nature, moving to the European market
- What do you see as major issues when comparing the current basically process-based regulations versus an alternative product-based regulations?

### *Traceability issues*

- Do you see possibilities for the development of event-specific methods for new gene-edited animal breeds?
- Do you see options for traceability of multi-edited animal breeds?
- Do you see possibilities for the traceability of specific traits? If so, what do you see as bottlenecks for adequate tracing of traits of potential concern?
- In your view, what should be the consequence of a possible product-based approach in terms of traceability, in other words, what would still be relevant for monitoring programmes?

### *Safety issues*

- What do you see as the major issue(s) when considering the safety of new gene-edited animal breeds?
- When moving from a process-based regulation to a more product-based approach, what should be the basic requirements in terms of safety of new animal products?
- Would your concerns be primarily related to the intended effects or to potential unintended effects?
- When considering multi-edited GMO events, could you think of situations where segregation of the edits in subsequent generations could lead to safety concerns?

### *Economic aspects*

- What are your main concerns in terms of economic effects of the increased application of NBTs? Specific examples?
- What do you see as the main economic opportunities of the application of NBTs? Specific examples?
- What are your main concerns in terms of economic effects of the current (regulatory) situation with relation to the application of NBTs in animal breeding, in a Dutch and/or European perspective?
- Where do you see possibilities to benefit from the current (regulatory) situation with relation to the application of NBTs in animal breeding, in a Dutch and/or European perspective?
- More in general, what are the fields of application of the NBTs that are the most relevant for the Dutch/ European situation? Specific examples? And are there alternative routes to reach the same goals without the use of NBTs? What would be the consequences of the alternative routes?

### *National / EU / global (regulatory) aspects*

- When looking at the international perspective, what are your main concerns related to the upcoming application of NBTs in animal breeding? What do you see as the major issues in this respect? Specific examples?

- Do you believe that harmonisation of regulatory requirements is important in this respect? Specific examples to underpin your conviction?
- What would be your preferred route of harmonising regulatory requirements? Who should take the initiative to come to harmonised requirements? Would you be willing to participate in meetings on harmonisation (should these be organised at some stage)?

## A1.3 Microbiology Sector

### *General developments in microbial biotechnology for the food/feed industry*

- What do you consider as the most important developments in microbial biotechnology for the food/feed industry? Specific examples?
- What do you see as the most beneficial developments? Specific examples?
- What do you see as developments of concern? Specific examples?
- What do you see as a realistic timeline for
  - gene edited micro-organism-containing or derived products moving to the European market based on base editing
  - gene edited micro-organism-containing or derived products moving to the European market based on HDR procedures
  - Synthetic biology products, with characteristics unknown to nature, moving to the European market
- What do you see as major issues when comparing the current basically process-based regulations versus an alternative product-based regulations?

### *Traceability issues*

- Do you see possibilities for the development of detection methods (PCR-based?) for gene edited micro-organisms?
- Do you see options for traceability of multi-edited micro-organisms?
- -Do you see possibilities for the traceability of specific traits? If so, what do you see as bottlenecks for adequate tracing of traits of potential concern?
- In your view, what should be the consequence of a possible product-based approach in terms of traceability, in other words, what would still be relevant for monitoring programmes?

### *Safety issues*

- What do you see as the major issue(s) when considering the safety of gene edited micro-organisms?
- When moving from a process-based regulation to a more product-based approach, what should be the basic requirements in terms of safety of new gene edited micro-organism-consisting or derived products?
- Would your concerns be primarily related to the intended effects or to potential unintended effects?

### *Economic aspects*

- What are your main concerns in terms of economic effects of the increased application of NGMTs? Specific examples?
- What do you see as the main economic opportunities of the application of NGMTs? Specific examples?
- What are your main concerns in terms of economic effects of the current (regulatory) situation with relation to the application of NGMTs in microbial biotechnology, in a Dutch and/or European perspective?
- Where do you see possibilities to benefit from the current (regulatory) situation with relation to the application of NGMTs in microbial biotechnology, in a Dutch and/or European perspective?
- More in general, what are the fields of application of the NGMTs that are the most relevant for the Dutch/ European situation? Specific examples? And are there alternative routes to reach the same goals without the use of NGMTs? What would be the consequences of the alternative routes?

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#### *National / EU / global (regulatory) aspects*

- When looking at the international perspective, what are your main concerns related to the upcoming application of NGMTs in microbial biotechnology? What do you see as the major issues in this respect? Specific examples?
- Do you believe that harmonisation of regulatory requirements is important in this respect? Specific examples to underpin your conviction?
- What would be your preferred route of harmonising regulatory requirements? Who should take the initiative to come to harmonised requirements? Would you be willing to participate in meetings on harmonisation (should these be organised at some stage)?

## A1.4 Social Sciences

#### *Perception*

- Which trends do you observe in the public perception of modern biotechnology?
  - For example, has there been a decline or increase in public acceptance?
- What are the determining factors for this perception of biotechnology?
  - For example, can these factors be related to attributes of the genetic modification process or the product, or to both?
    - Example: recombinant DNA being 'unnatural' and therefore perceived as risky
  - What role does safety play in this?
    - In addition, what is the trust in the safeguarding of and reassurances over safety by the authorities and legislators?

#### *Policy*

- Precautionary principle: How is the principle affected by a transition from process- to product-based legislation?
- Innovation: How will it be impacted by such a transition from process- to product-based legislation? Which innovations might be boosted or thwarted?
- Sectors (Agro, Pharma, Industrial): To what extent can different approaches be followed for different sectors?

#### *Role of social sciences*

- Role of ethics: what roles do you see, including new ones?
- To what extent are participatory methods applicable, e.g. consensus conferences, to decide on a shift in legislation?

#### *Legislation*

- What regulatory foundation do you envisage for a product-based legislation?
  - For example, would an extension of the 'novel foods' legislation be possible?
- To what extent is alignment with legislation of other countries needed?
- How much resilient will a new product-based legislation be as compared to a process-based one?
- At what timescale do you expect such a change from process- to product-based legislation to take place, if at all?

#### *Ethics*

- Are these proposed changes reconcilable with ethical principles?
  - For example, would this not conflict with the Dutch stance on animal biotechnology (dismissive of animal biotech for the purpose of productivity increase)
  - Is an ethical assessment still possible?

## Annex 2 List of interviewed experts

Name	Function	Institution or company	Sector
[REDACTED]	[REDACTED]	Hendrix Genetics	Animal
[REDACTED]	[REDACTED]	CRV Arnhem	Animal
[REDACTED]	[REDACTED]	Biotechnology and Society, TU delft	Social
[REDACTED]	[REDACTED]	Consumer behaviour, WUR	Social
[REDACTED]	[REDACTED]	Law Group social sciences, WUR	Social
[REDACTED]	[REDACTED]	Royal van Zanten	Plant
[REDACTED]	[REDACTED]	Centre for Genetic resources, Wageningen Livestock Research	Animal
[REDACTED]	[REDACTED] [REDACTED]	Biobased Products, Wageningen Food & Biobased Research / Industrial Molecular Microbiology, UvA	Microbiology
[REDACTED]	[REDACTED]	Topigs Norsvin	Animal
[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	Corbion / Bacterial Cell Factories, WUR	Microbiology
[REDACTED]	[REDACTED]	Protein brewery	Microbiology
[REDACTED]	[REDACTED]	Plantum	Plant
[REDACTED]	[REDACTED]	Bioscience, Wageningen Plant Research	Plant
[REDACTED]	[REDACTED]	Technology and International development, WUR	Social
[REDACTED]	[REDACTED] [REDACTED]	Netherlands Commission on Genetic Modification (COGEM)	Social
[REDACTED]	[REDACTED]	Microbiology, WUR	Microbiology
[REDACTED]	[REDACTED]	Mushroom Research, Wageningen Plant Research	Microbiology
[REDACTED]	[REDACTED] [REDACTED]	DSM	Microbiology
[REDACTED]	[REDACTED]	Industrial Microbiology TU Delft	Microbiology
[REDACTED]	[REDACTED]	Animal Health & Welfare Department, WUR	Animal
[REDACTED]	[REDACTED]	Plant breeding, Wageningen Plant Research	Plant
[REDACTED]	[REDACTED] or	Molecular plant physiology, UU	Plant
[REDACTED]	[REDACTED]	Rijk Zwaan	Plant
[REDACTED]	[REDACTED]	Alta Genetics	Animal

## Annex 3 Overview interviews

The interviews were held as a conversation between interviewer and interviewee. In most interviews, not all questions were discussed, depending on the expertise of the interviewee and/or on answers on earlier questions, indicated with 'not specifiek behandeld'. Questions or comments of the interviewers (indicated with the initials of the interviewers: 5.1.2 e5.1.2 e) are reported in some interviews, to indicate that topics were not brought forward by the interviewee. Reports were made of the interviews, and these reports were sent to the interviewee to be checked for correct reporting of views and answers. The reports were made in the language the interview was held in. In this Annex, answers are grouped under the correct questions as much as possible, and were used as such for the sections 'expert interviews' in the main report.

This Annex was added as extra background information for the sponsor, and it was agreed that no translation of interviews was needed.

De interviews zijn zo veel mogelijk als een gesprek tussen geïnterviewde en interviewers gehouden. In de meeste interviews zijn niet alle vragen aan bod gekomen, afhankelijk van expertise en eerdere antwoorden zijn bepaalde vragen overgeslagen, hieronder aangegeven als 'niet specifiek behandeld'. De initialen van de interviewer(s) (i 5.1.2 e5.1.2 e5.1.2 e) staan vermeld in een deel van de antwoorden, waarmee wordt aangegeven dat onderwerpen niet door de geïnterviewde, maar door de interviewer zijn aangedragen. De verslagen van de interviews zijn aan de geïnterviewden voorgelegd voor een check of de visies en antwoorden juist gerapporteerd zijn. De verslagen zijn opgesteld in de taal waarin het gesprek plaats heeft gevonden. Uit ieder verslag zijn de relevante antwoorden zo veel mogelijk onder de desbetreffende vraag bij elkaar geplaatst, en op basis van de gecombineerde antwoorden zijn de secties uit het verslag geschreven.

Deze Annex is als extra achtergrond toegevoegd na overleg met de sponsor, en er is afgesproken dat er geen extra vertaling of standaardisering van de interviews gedaan zou worden.

### A3.1 Plant Sector Interviews

#### A3.1.1 Developments

<i>Q: What do you consider as the most important developments in plant breeding? Specific examples?</i>	
P1	Er vindt een verschuiving plaats van conventionele transgenese in planten naar CRISPR-Cas mutagenese, voornamelijk voor het uitschakelen van genen door NHEJ (geen gene editing? HDR wel als gene editing beschouwen, ODM kan wel gene editing zijn).
P2	Nieuwe technieken die veel potentie hebben voor productverbetering, bijv CRISPR-Cas. Die potentie kan nauwelijks benut worden voor producten in de EU, door de uitspraak van het Europese Hof. Ter illustratie: er wordt veel onderzoek gedaan naar vatbaarheidsgenen. Dat zijn genen bijvoorbeeld in een plant, die door een pathogeen worden gebruikt/misbruikt tijdens de infectie. Zo'n gen maakt de plant vatbaar. Als een vatbaarheidsgen wordt uitgeschakeld, wordt de plant resistent tegen dat pathogeen. Gevolg: een sterkere plant, waardoor er mogelijk minder bestrijdingsmiddelen hoeven te worden gebruikt. Nu wordt er in de onderzoeksfase CRISPR-Cas toegepast om het kandidaatgen uit te schakelen en te kijken of de resistentie daadwerkelijk toeneemt. Als dat het geval is, vraagt een veredelaar hier in EU, vanwege de GMO regelgeving, geen markttoelating aan voor de plant. De veredelaar gebruikt een toegestane klassieke mutatietechniek (ongericht) en gaat in grote hoeveelheden planten op zoek naar de juiste mutant waarin het betreffende gen is uitgeschakeld. (Extra uitleg van P2: Meestal worden maar 1 of enkele planten gemutageniseerd. Vervolgens worden daar zeer veel nakomelingen (families) van gegenereerd waarin de mutaties uitsplitsen. Die families worden getest.) Dit kost heel veel extra tijd (en geld). En omdat de klassieke mutagenese minder gecontroleerd is, en er naast de gezochte mutatie nog veel meer mutaties zijn, is deze techniek ook minder veilig.
P3	Van oudsher tedious business, introductie nieuwe rassen kost jaren, DNA markers en WGS hebben dit versneld. Maar, veredeling is altijd afhankelijk geweest van kans-processen, een mutatie die toevallig in een gen optreedt, bijvoorbeeld door een natuurlijke mutatie of als gevolg van stralingsmutagenese. Met genome editing is dit

	radicaal veranderd. Eerst met TALEN en nu met het zeer efficiënte Crispr-cas, zijn gerichte edits mogelijk; dit is relatief snel en goedkoop. Bevindingen uit fundamenteel onderzoek kunnen nu heel snel ook in veredeling gebruikt worden, in het verleden was dit vaak uiterst lastig.
P4	<ul style="list-style-type: none"> <li>• Meest veelbelovende techniek is gene-editing. Maar in groente kost het veel moeite om 'new breeding techniques' (NBTs zoals gene editing) aan de gang te krijgen.</li> <li>• Kost veel tijd om op grote schaal gene-editing toe te passen.</li> <li>• Noemt service providers die gene edited gewassen ontwikkelen voor veredelaars.</li> </ul>
P5	<ul style="list-style-type: none"> <li>• de sierteeltsector heeft een grote afzetmarkt in Europa. We zitten in segment waar de beleving een belangrijke rol speelt</li> <li>• afzet via retail; op voorhand zijn er een aantal elementen die invloed hebben op de business <ul style="list-style-type: none"> <li>o bijvoorbeeld, restrictie op gewasbestrijdingsmiddelen</li> </ul> </li> <li>• ze gebruiken mutatieveredeling (bijvoorbeeld voor kleurverandering)</li> <li>• problemen met ziektes en plagen zorgen voor een druk op onze teelt</li> <li>• GMO's: retail wil het liever niet, omdat het een negatief effect op verkoop van planten. Maar zolang dit onder de radar blijft, leidt dit niet tot uitsluiting. GM bloemen zijn al op de markt in Nederland (blauwe anjers van een ander bedrijf)</li> <li>• als je als sector wil overleven, dan moet men op langer termijn aan de duurzaamheids- eisen kunnen voldoen.</li> </ul>
P6	<p>Ontwikkelingen die selectie efficiënter &amp; effectiever maken:</p> <ul style="list-style-type: none"> <li>-Robot-phenotyping: Big data, artificial intelligence gebruiken voor DNA analyse</li> <li>-Het koppelen DNA &amp; fenotypische data --&gt; zorgt voor verbeterde selectie.</li> <li>-Gene function analyse met CRISPR-Cas</li> </ul> <p>Daarnaast komt er, naast aandacht voor simpele traits, steeds meer interesse voor complexe traits (zoals in de mais), inclusief Polyploidy analyse.</p> <p>Gene editing kan bijdragen aan het creëren diversiteit; ook bedrijven kijken hiernaar. (In EU minder spannend dan elders.)</p> <p>Er is al een scheiding tussen gene editing voor onderzoek en voor productie voor planten.</p> <p>Achtergrond: Plantenveredeling heeft zich in de loop van de tijd ontwikkeld. Het is sterk toepassingsgericht en absorbeert nieuwe ontwikkelingen, zoals moleculaire biologie. Nieuwe ontwikkelingen zijn o.a. beeldanalyse, high-throughput fenotypering en kunstmatige intelligentie. Tegenwoordig vindt veredeling vooral plaats door snellere introgressie (o.a. van verre verwanten uit het wild of de genenbank) met behulp van marker-assisted selectie, naast veel mutatieveredeling zoals door chemische mutagenese met EMS.</p> <p><i>Q: What do you see as the most beneficial developments? Specific examples?</i></p>
P1	Met het idee dat CRISPR-Cas mutagenese ook meer acceptabel zal zijn. Meer nadruk op korte termijn op gemutageniseerde planten. Bijvoorbeeld glutenvrije tarwe, wellicht mogelijkheid om toch goede bakkwaliteit te hebben.
P2	Niet specifiek behandeld
P3	Targeted, vooraf gewenste mutaties in bepaalde genen. Kunnen base-edits zijn, maar ook epigenetische veranderingen zijn mogelijk, er kan nu gericht worden gewerkt.
P4	Niet specifiek gevraagd
P5	<ul style="list-style-type: none"> <li>• nieuwe gentechnieken kunnen zorgen voor: o duurzaamheidsoplossingen o het ontwikkelen van nieuwe producten. Maar dat zorgt ook voor problemen. Als je het bestaand assortiment wil wijzigen, moet men kijken naar de regelgeving. Dit brengt kosten met zich mee. Het is een langdurig proces o bij polyploide gewassen kan men met gene editing meerdere allelen tegelijk editen. Is een voordeel, maar tegelijkertijd ook een uitdaging.</li> <li>• Voorkeur: gericht versoepelde toelating op non-food eigenschappen, dus die geen potentiële schade kunnen aanrichten aan de gezondheid van de mens</li> </ul>
P6	Alle bovenstaanden. Snelheid van selectie en verkrijgen van veredeling, waar ook Crispr CAS een rol bij kan spelen. De verdelingssector kan sneller nieuwe gewassen ontwikkelen die aan veranderende maatschappelijke wensen kan voldoen (bijvoorbeeld het gebied van consumentengemak, klimaatverandering/verduurzaming; vermindering gebruik chemische middelen).
	<i>Q: What do you see as developments of concern? Specific examples?</i>
P1	P1 ziet die niet. Producenten zullen geen risico's nemen. Voor mensen die gene-editing als GGO beschouwen, zal dat nog een probleem kunnen zijn. Nav vraag: bedrijven moeten verantwoordelijk zijn voor hun producten – moeten het wel kunnen bespreken met autoriteiten – geen oplossing hiervoor.
P2	Niet specifiek behandeld
P3	Die zijn er niet niet, geen issues qua veiligheid. Voorheen werd alles bestraald, wat veel meer mutaties oplevert, producten daarvan worden zomaar op de markt gezet. Waarom zou er nu wel een issue met veiligheid zijn? Ook vergeleken met natuurlijke mutaties, die hebben zover bekend de afgelopen tienduizend jaar nooit gevaren gebracht. Bovendien, met genome editing voorkom je linkage drag (het meekomen van ongewenste eigenschappen, wat je met traditionele methoden hebt.



P4	Niet specifiek behandeld
P5	<p>· We hebben te maken met industrie die voorzichtig is. Het bestaande assortiment kun je niet makkelijk aanpassen. Zij willen dit wel om industrie duurzamer te maken. · ongericht muteren betekent testcycli doorlopen om resistenties te kunnen vinden (S genen). · Probleem: sterk heterozygote background. Gene editing zou voordeel zijn om mutaties aan te brengen.</p>
P6	Niet specifiek behandeld
<i>Q:What do you see as a realistic timeline for: CRISPR-Cas / gene edited plant products moving to the European market based on base editing?</i>	
P1	: Ongeacht of dit gaat via huidige traject of via nieuw traject 5-10 jaar. Mogelijk sneller in de bulkproducten. Bij gebruik van HDR-toepassing – mogelijk iets langer, wel vergelijkbaar.
P2	<p>■ Bijv. binnen 1-3 jaar? P2: Ik denk dat dit wel mogelijk is voor veevoer, misschien voor non-food toepassingen. Ik verwacht niet voor voedseltoepassingen, vanwege de Europese regelgeving. Net als nu met GMO gewassen: er wordt heel veel GMO soja, mais en katoen geïmporteerd voor veevoer. P2 verwacht geen non-browning appels op Europese Markt</p>
P3	<p>Editing om drie redenen, voor opbrengst, gezondheid en duurzaamheid. Ontwikkeling van nieuwe producten gericht op consument; edited soya high-oleic acid olie is al meer dan een jaar op de markt in de VS. Willen we de EU burger gezonde producten onthouden? Komt wellicht wel naar de EU: het is niet detecteerbaar en in veel regio's in de wereld zijn edited gewassen wel toegestaan. Komt sowieso naar Europa in processed foods als ingrediënt. Andere voorbeelden van producten van gene edited planten die eraan komen zijn gene-edited tarwe zonder gluten, geschikt voor consumenten met coeliakie en tarwe met veel meer voedingsvezel in het meel. Het gaat wel jaren duren voordat het op de EU markt komt (na juridisch procedures). Er zijn enorme ontwikkelingen in China met gene edits in planten, er worden zeer veel patenten aangevraagd, zo'n 60% van alle editing patenten wereldwijd komen uit China. Producten uit andere landen zullen uiteindelijk ook verhandeld worden naar de EU.</p>
P4	Niet specifiek behandeld
P5	Niet specifiek behandeld
P6	<p>Is als in een kristallen bol naar politiek kijken. Rapportage van de Europese Commissie in April 2021--&gt; is dat alleen een idee van wat speelt, of zijn er ook al scenario's? Als er al scenario's worden voorgelegd zou binnen 5 jaar zou in de wet veranderd kunnen zijn (bijvoorbeeld een wetenschappelijk onderbouwde uitzondering voor SDN-1/2). In de farm to fork strategie zit een haakje voor mogelijke aanpassing, om verduurzaming mogelijk te maken. Dit geldt voor SDN-1 en SDN-2 producten, niet voor nieuwe transgene gewassen.</p>
<i>o CRISPR-Cas / gene-edited plant products moving to the European market based on HDR procedures</i>	
P1	Niet specifiek behandeld
P2	Niet specifiek behandeld
P3	<p>Voor SDN2 editing zonder transgen, geldt hetzelfde, deze worden al geproduceerd en uiteindelijk worden deze waarschijnlijk ook verhandeld naar de EU. Met grotere stukken DNA/transgen wordt het als GMO geklassificeerd en gereguleerd, logisch; maar in dat geval zou dat ook niet een probleem hoeven zijn ook hier zijn geen veiligheidsissues. EFSA heeft al vele GMO aanvragen van een positief advies voorzien</p>
P4	Niet specifiek behandeld
P5	Niet specifiek behandeld
P6	<p>Zie boven voor SDN-1/2; voor SDN-3 (transgenese) zal dit zal nog vele jaren duren; zullen GMO blijven. (Overigens: er is nu 25-35 jaar ervaring met transgene planten. In praktijk geen negatieve gevolgen gevonden. Dus: Is er een probleem met veiligheid? Laatst een publicatie doorgestuurd naar ■ met deze vraag) ■ Nooit volledig productbased?</p> <p>Ik denk het niet. In Canada lopen ideeën voor een stukje inbouwen voor procesbased in de regelgeving. Discussie over 'what is significant change' is daar gaande.</p>
<i>Synthetic biology – derived plantproducts, with characteristics unknown to nature, moving to the European market?</i>	
P1	<p>zal nog wel stuk langer duren wanneer het niet meer in de natuur voorkomt. Beter in tabak produceren, het gebruik van tabaksplant als 'fabriek' zal geen probleem geven voor voedselveiligheid. Chassis planten: beter bacteriën gebruiken als chassis voor de productie van gewenste moleculen, wellicht een eukaryoot (gist/filamenteuze schimmel) als bepaalde processing modificaties (e.g. glycosylering) nodig zijn. Newcotina – Diego Azarez, Valencia – productie van nieuwe stoffen in tabak.</p>
P2	Niet specifiek behandeld
P3	Synthetische biologie, vereist wel enige controle en dus ook regulering; al betekent dat niet dat producten van synthetische biologie onveilig zijn; gaat wel jaren duren.
P4	Niet specifiek behandeld
P5	Niet specifiek behandeld
P6	Als SDN-3 hierboven



<i>Q: What do you see as major issues when comparing the current basically process-based regulations versus an alternative product-based regulations?</i>	
P1	fundamenteel ziet P1 geen probleem- wanneer je alles gaat beoordelen – balans nodig voor wat je wel en niet beoordeelt.
P2	Niet specifiek behandeld
P3	Aan beide kanten kleven voor- en nadelen; precieze juridische context lastig te duiden, dus kan hier geen precies antwoord op geven. Maar als wij onze EU regelgeving niet aanpassen, dan worden we een 'museum', als we internationaal niet mee kunnen doen lopen belangrijke stakeholders in de groene sector weg. Er zal altijd wel wat alternatief geproduceerd blijven worden, maar dat blijft zo ook een niche markt. EU moet een beter innovatiebeleid initiëren, er is onvermogen van de EC om dit te reguleren. Er zou verandering kunnen komen maar dat duurt nog wel even: de Europese Raad heeft EC gevraagd om dit uit te zoeken. Via questionnaires, EC zal hier iets mee moeten doen, zodat Europese bedrijven een kans hebben en moet door het EP, gaat nog wel jaartje of 3 duren.
P4	Niet specifiek behandeld
P5	Niet specifiek behandeld
P6	<p>Op dit moment: analyses zijn product based zodra ze de eerste zeef op basis van methode (GM of niet) gepasseerd zijn, maar we toetsen(analyseren) tegenwoordig alleen producten die met een bepaalde methode (GM) gemaakt worden.</p> <p>Als we alles product gaan toetsen --&gt; waar leg je dan een grens? Op de stelling: 'Productbased is veel wetenschappelijker' --&gt; dat kan; ligt aan waar je de grens van een product dat getest moet worden? Alle ~1200 rassen die jaarlijks op de markt komen toetsen lijkt me niet haalbaar, en een onnodige uitbreiding van safety assessments. Dus met een product-gebaseerde regelgeving is er de kans dat er niet minder, maar meer dure veiligheidsonderzoeken nodig zijn. Dit kan o.a. voor een afname in diversiteit in gewassen zorgen, wat juist indruist tegen allerlei duurzaamheidsdoelen. Andere fundamentele kwestie: Waar in de keten moet je voedselveiligheid waarborgen? Gen, ras, wat een boer oogst, wat na verwerking is, wat er op het bord ligt? In principe op het bord, maar dat is niet haalbaar, ook niet na de boer. Daarom wordt een ras getoetst. Dat hoeft niet logisch te zijn om dat er bijvoorbeeld ook een effect op veiligheid elders in de keten kan zijn, zoals effecten van bemesting en processing. Vice versa kan de genetika van het ras ook een effect hierop hebben, zoals bij acrylamide vorming in de aardappel. Het 'product' is dan een bepaalde eigenschap binnen een specifieke achtergrond. Dat is wellicht relevant voor complexe traits maar niet haalbaar voor o.a. kleine veredelaars.</p>

### A3.1.2 Traceability

<i>Q: Do you see possibilities for the development of event-specific methods for new gene-edited crop plant varieties?</i>	
P1	Kan door gebruik van DNA barcodes maar uniekheid zal niet meer gegarandeerd zijn. In theorie zal random integratie ook niet meer te volgen zijn.
P2	<i>P2 Bij de traceerbaarheid van kleine mutaties zie ik niet dat het mogelijk zal zijn om hier event-specifieke methoden voor te ontwikkelen, de vraag is ook of dat nodig is</i>
P3	Nee, niet te onderscheiden van natuurlijke mutaties
P4	o In de toekomst wellicht meer interesse voor gene-editing, in de huidige situatie is gene-editing gereguleerd als GMO techniek maar het verschil tussen een natuurlijke mutatie en mutatie teweeg gebracht door NBT aantonen is nu niet mogelijk.
P5	· Bij snijbloemen en potplanten, in hoeverre speelt traceerbaarheid daar mee? [ ] noemt Petunia (incident met niet-toegelaten GGO) als voorbeeld o in de keten, vanaf uitgangsmateriaal tot verkoop wordt bijgehouden waar iets waar vandaan komt. Er zit een heel stuk traceerbaarheid in. o als de nieuwe gentechnieken worden ingevoerd dan zal dit zo blijven
P6	Traceability is een heel lastige kwestie. Mondiaal opererende bedrijven: ook al zouden ze helemaal transparant willen zijn, kan alleen over wat zij met het materiaal hebben gedaan. Achtergrond van lijnen, bijv. uit Argentinië, kan niet bekend zijn. Dit in tegenstelling tot transgene 'events'
<i>Q: - Do you see options for traceability of multi-edited plants?</i>	
P1	- op specifieke locatie PCR en sequenzen, dit kan op meerdere locaties maar dat moet je deze locaties wel weten - specifieke primers ontwikkelen voor alle targets.
P2	Als een risico in genoom herkenbaar is, dan moet je er een test voor hebben, bijvoorbeeld PCR-gebaseerd. Maar als het product ook bereikt had kunnen worden met klassieke veredeling is zo'n test niet nodig.
P3	Nee, bij multiplex edits is, bijvoorbeeld, ook nooit te bewijzen dat het niet natuurlijke mutaties zijn.
P4	Niet specifiek behandeld
P5	· Essentieel punt: gene editing wordt vaak gekoppeld aan natuurlijke mutanten. Maar in onze gewassen zouden wij graag nieuwe unieke veranderingen willen inbrengen (die mogelijk nog niet in de natuur

voorkomen) die deze problemen (ziekten en plagen) oplossen. Deze eigenschappen zullen hierdoor ook traceerbaar zijn, niet alleen genetisch maar bijvoorbeeld ook een resistent fenotype.

**P6 Technically yes – practically no (why would you if it cannot be enforced??)**

*Q: Do you see possibilities for the traceability of specific traits? If so, what do you see as bottlenecks for adequate tracing of traits of potential concern?*

P1 - Schaal van makkelijk zichtbare traits – tot onzichtbare eigenschappen (e.g. resistentie tegen stress). Modificatie van bestaande genen eenvoudiger, bij transgenese is een vergelijkende analyse nodig. Wanneer je zoekt vindt je de modificatie wanneer er voldoende sequentie-informatie is.

P2 Niet specifiek behandeld

P3 Alleen als de fabrikant meelevert wat er precies is geedit zou je dit kunnen volgen. Onwaarschijnlijk dat dit gebeurt.

P4 Niet specifiek behandeld

P5 Niet specifiek behandeld

P6 Niet specifiek behandeld

*Q: In your view, what should be the consequence of a possible product-based approach in terms of traceability, in other words, what would still be relevant for monitoring programmes?*

P1 Voor de veredeling wat is van belang om te kunnen traceren. Veredelaar zou marker willen kunnen volgen om te zien welk cultivar het is. – huidige markers zijn veelal op SNPs gebaseerd. – representatieve SNPs.

P2 Zolang de producten ook met klassieke veredeling bereikt kunnen worden, laat dan los dat het op veiligheid beoordeeld moet worden.

P3 Niet specifiek behandeld

P4 Niet specifiek behandeld

P5 - Maar wij willen niet product in de winkel zetten waar rumoer over ontstaat (producten die illegaal zijn). Als het om planten gaat wil men geen enkel risico lopen

P6 Any registered novel trait can indeed be traced

### A3.1.3 Safety

*Q: What do you see as the major issue(s) when considering the safety of new gene-edited crop plant varieties?*

P1 veranderde inhoudsstoffen bij veranderde metabole routes – zal eruit gevestigd worden voor de markt – toepassing van crispr-cas versneld domesticeren van interessante (wilde) planten (bijv rijst dat kan groeien op zoute bodem), over de wilde planten is wellicht minder bekend en dus onbekende risico's – focus op negatieve stoffen is dan belangrijk. Geldt ook voor bestaande gewassen – daar is het veelal al een aandachtspunt – niet waarschijnlijk dat het daar mis kan gaan – genoeg kennis van onderliggende metabole routes. OECD consensus documenten kunnen leidraad zijn.

P2 Niet specifiek behandeld

P3 Geen, geen verschil met traditionele gewassen.

P4 Niet specifiek behandeld

P5 Niet specifiek behandeld

P6 For mutants: there are always safety issues with off-targets, just like with natural mutants. I don't see safety issues with targeted changes as these are things we know

*Q: - When moving from a process-based regulation to a more product-based approach, what should be the basic requirements in terms of safety of new plant products?*

P1 Veiligheidsbeoordeling dient realistisch en proportioneel te gebeuren, en science-based. De beste mogelijkheid zie ik daarvoor bij een product-gebaseerde beoordeling: het gaat om de veiligheid van het product. Nu bij een transgene beoordeling, is de veiligheidsbeoordeling doorgeschoten: niet omdat er veel risico's zijn, maar vanwege de grondhouding van mensen die tegen gebruik van GM technieken in gewassen zijn.

P2 Niet specifiek behandeld

P3 Ik zou niet weten welke, requirements worden nu ook al worden ge-eist door bv. voedselautoriteiten, vrij van toxines, etc.

P4 Niet specifiek behandeld

P5 o Het belangrijkste punt is, uitzoeken wat het mechanisme is. Voorbeeld: aardappels met resistentie voor aaltje. Efficiënte resistentie kan gekoppeld zijn aan een toxisch effect. Je kan het niet uitsluiten. Daarom is kennis van het mechanisme is van belang

P6 Speed, cost and legal certainty

*Q: Would your concerns be primarily related to the intended effects or to potential unintended effects?*

P1 - Meer zorgen bij mogelijk denkbare intended effects, vooral als edits steeds 'exotischer' worden – niet zozeer bij unintended effects. – bij gangbare voedselgewassen.

P2	(Niet bij unintended, want:) Bij de huidige mutatieveredeling, zoals met EMS, is 99.9% van de effecten unintended. Dat is oké in de regelgeving, maar dat is ongebalanceerd, want met nieuwe technieken zien we nauwelijks unintended effecten. Bij planten is beoordeling van unintended effecten onzinnig. Bij klassieke mutagenese en bij gewone kruisingsveredeling met wilde verwanten wordt er ook niet naar gekeken, – soms zijn er wel 10.000 tot 100.000 SNPs mutaties bij die technieken. Er wordt wel naar fenotypische gevolgen gekeken door de veredelaar. Die kijkt sowieso niet alleen naar de veranderde eigenschap, maar ook naar secundaire effecten: zijn er negatieve effecten, is het product goed voor de consument, zijn er geen ongewenste effecten. Inherent meegenomen in plantveredeling, geen regelgeving van overheid voor nodig. Nu met crispr cas, wordt er bij planten wel naar gekeken. Dat is onevenwichtig. Voor unintended effecten bij planten – geen aandacht aan geven in de regelgeving. Ik denk dat dit heel anders ligt bij mensen, als je praat over medische toepassingen. Dan moet je heel goed kijken of er geen bijeffecten zijn, bijv. kankerverwekkend effect van een therapie.
P3	*Niet gevraagd, niet relevant op basis van eerdere antwoorden*
P4	Niet specifiek behandeld
P5	<ul style="list-style-type: none"> <li>o Met normale mutagenese, alles wat afwijkt van het normale fenotype, dat gooi je weg</li> <li>o Je kunt heel specifiek zoeken naar bijv bloemkleur type. De kans op negatief effect is zeer klein</li> <li>o Met de nieuwe gentechnieken kun je heel specifieke mutaties aanbrengen. Bijvoorbeeld: <ul style="list-style-type: none"> <li>§ pathway-specifieke mutanten maken. § een specifiek gen upreguleren</li> <li>§ de bedoelde effecten zijn inzichtelijk. Maar je moet goed weten wat je doet; er kunnen pleiotrope effecten ontstaan. Deze moeten goed onderzocht worden</li> </ul> </li> </ul>
P6	Broertje dood aan discussie over unintended effects--> Deze zijn superbelangrijk in dieren en mensen; in plantenveredeling niet. In de veredeling selecteer je, en planten met (ongewenste) off-targets worden niet geselecteerd; dat doe je ook in gewone veredeling. Veredeling is de 'kunst van het weggooien'
<i>Q: When considering multi-edited GMO events, could you think of situations where segregation of the edits in subsequent generations could lead to safety concerns?</i>	
P1	Segregatie van edits – zou bij de ontwikkeling een aandachtspunt moeten zijn- gecombineerde modificaties zouden gegroepeerd moeten zijn. Aardappel – reductie van glycoalkaloiden – gedaan in Japan – P1 stuurt link door
P2	Lastig in veredeling, Polygene eigenschappen segregeren ook in de nakomelingen, in die zin is het niet anders wanneer je het hebt over multi-edits die over verschillende genen zijn verspreid. Het levert geen extra risico op.
P3	*Niet gevraagd, niet relevant op basis van eerdere antwoorden*
P4	Niet specifiek behandeld
P5	Niet specifiek behandeld
P6	Je moet eigenschappen in hun genetic background zien. Uitsplitsen (segregatie) van complexe traits is ook een issue in de huidige veredeling. Bij een nieuw ras moet je laten zien dat eigenschappen stabiel zijn.

### A3.1.4 Economic consequences

<i>Q: What are your main concerns in terms of economic effects of the increased application of NBTs? Specific examples?</i>	
P1	Bijvoorbeeld de ontwikkeling van consumentvriendelijke tomaat die een enorm succes wordt kan economische verhoudingen doen verschuiven wanneer ze die bijvoorbeeld in Amerika zouden gaan eten. NL veredelaars zouden gene-edited planten in een dependance kunnen ontwikkelen in de VS
P2	*niet behandeld, buiten de expertise*
P3	het huidige klimaat in Europa waarin het gebruik van NBTs niet is toegestaan, zal de groene sector steeds meer verschrompelen, over 20-40 jaar zal de Europese groene sector niches bedienen. Studenten die geïnteresseerd zijn in 'groene biotech' zullen weglopen, overstappen naar de 'rode biotech', of misschien naar buiten Europa. Ook veredelaars zullen wegtrekken, en de teelt zal niet meer competitief zijn. BASF en Bayer besloten bijvoorbeeld direct na de uitspraak van het Europese hof om innovatie te verplaatsen.
P4	Voor de firma is van belang wat de maatschappij vind van aanpassen regelgeving. Wat vinden boeren, supermarkten, (processing)bedrijven en de consument hiervan? Het is belangrijk om met bedrijven mee te denken en hierbij consument en andere stakeholders mee te nemen. Op deze manier draagvlak in de maatschappij creëren o Nadeel is dat nu alleen grote bedrijven GM producten op de markt brengen, dus de grote GM landbouwgewassen. Octrooien zijn vak ook in handen van dit soort grote spelers, kunnen gene-edited gewassen van wel op de markt komen? Dit kan belemmerend werken voor kleine spelers. o Noemt segmentatie in de groente sector met een groot palette en veel gevarieerde traits.
P5	· Zij produceren in Nederland voor Europa. En in Colombia voor de VS; in de VS is gene editing sterk in ontwikkeling · Andere bedrijven die hun ip pakken, kunnen genetische variëteit creëren en zouden een bedreiging kunnen vormen · en via een omweg kunnen producten in Europa komen. Dit zou een impact hebben op de Nederlandse telers
P6	Probleem: patenteerbaarheid; overregulatie (bij GMO'S) ondanks winst die in duurzaamheid behaald kan worden Concentratie in de sector, de grote bedrijven hebben de middelen om de aan de regelgeving te voldoen.



Q: What do you see as the main economic opportunities of the application of NBTs? Specific examples?	
P1	*niet behandeld, buiten de expertise*
P2	*niet behandeld, buiten de expertise*
P3	Veredelaars hebben lange wensenlijsten voor aanpassingen aan gewassen. Stel je wilt een zoete tomaat, hiervoor bestaan natuurlijke mutaties, maar met CRISPR is het mogelijk in korte tijd (minder dan een jaar) in vele bekende tomatenvarianten deze mutatie te introduceren, anders zou je dat via kruisingen moeten doen wat een enorme klus is die decennia duurt. Daarnaast: nieuwe gewassen kunnen versneld worden gedomesticeerd. Innovatie op het gebied van gene editing is in NL in minimaal; elders met name in de VS is men al veel verder. Een aantal nieuwe bedrijven, zoals Calyxt, kunnen nu zelf gewassen editen – grote innovatiegolf. Bedrijven in de EU hebben niet de mogelijkheid om deze technologie te vermarkten. Kleine bedrijven hebben weinig kans, en daardoor zie je weinig innovatie (competitie voor multinationals, bijvoorbeeld door innovatieve start-ups, gebeurt hierdoor niet).
P4	Niet specifiek behandeld
P5	• Belang sierteelt sector: om straks te kunnen voldoen aan normen (duurzaamheid) • Vanuit de keten is er druk om problemen op te lossen d.m.v. van genetic solutions. M.b.v. veredelingstechnieken wordt het lastig. Nieuwe gentechnieken kunnen een belangrijke rol daarin spelen
P6	Er kan sneller zaad van betere kwaliteit worden gemaakt, en ook sneller gedeeld. Ook boeren en partijen betrokken bij de verwerking kunnen sneller meedelen in de waarde van de eigenschap. -Een bijdrage leveren aan de duurzaamheid.
Q: - What are your main concerns in terms of economic effects of the current (regulatory) situation with relation to the application of NBTs in plant breeding, in a Dutch and/or European perspective?	
P1	vaak nog geen grootschalige productie in de VS voor tomaten bij kleinere producten -NL veredelaars zouden hun leidende positie kunnen verliezen.
P2	In NL hebben we een hele sterke plantenveredelingssector, met name de groentezadensector. Denk bijvoorbeeld aan [REDACTED] of Bejo: oorspronkelijk Nederlandse bedrijven, nu internationaal werkend. We hebben nog steeds een van de beste posities ter wereld in deze sector, en handhaving van die positie is mogelijk - ondanks de uitspraak van het Europese hof mbt GMO & mutagenese technieken. Wereldwijd zien we een toename van de groenteconsumptie, NL kan zaden ontwikkelen. In de zaadsector zie je dat alle bedrijven in principe groeien. Als de EU regelgeving minder streng zou zijn, zou het nog beter gaan met bedrijven (is mijn verwachting). Nu echter: geen sprake van level playing field wereldwijd - Europa dreigt op achterstand te komen, omdat gebruik van nieuwe technieken hier door de regelgeving wordt afgeremd [REDACTED] Worden ook ontwikkelingen / delen van ondernemingen verplaatst? P2: in Amerika zijn de regels soepeler. Echter, het is niet zo dat alle activiteiten en ontwikkelingen zomaar verplaatst worden. Er is bij productie een risico op vermenging van 'gewone' en 'NBT aangepaste' gewassen. Als een organisatie zoals Greenpeace ontdekt dat de laatste per ongeluk op de Europese markt komt, kan dat heel veel schadeclaims geven. Daarom is men ook terughoudend in Amerika, ook internationale zaadproducenten zijn bang voor imago schade en schadeclaims.
P3	*Zie antwoord hierboven*
P4	[REDACTED] vraagt door over octrooirecht o noemt Europese octrooibureau besluit over octrooien op natuurlijke mutaties; in de EU zijn er geen patenten mogelijk op inkruisbare eigenschappen, in de USA wel o Je zou bijna een tweede non-GMO bedrijf op moeten gaan zetten, dit is economisch niet haalbaar
P5	• Retail: lastig in te schatten, bloemen zijn een serviceproduct Zie boven
P6	Like with GMO – innovation and innovators (human resources) will leave Europe, which is a serious drain for the Dutch sector(all field crops breeding, where GMO is dominant in the world - has left)
Q: Where do you see possibilities to benefit from the current (regulatory) situation with relation to the application of NBTs in plant breeding, in a Dutch and/or European perspective?	
P1	*niet specifiek aan bod gekomen*
P2	*niet behandeld, buiten de expertise*
P3	Niet specifiek behandeld
P4	Niet specifiek behandeld
P5	Niet specifiek behandeld
P6	None – with transgenes, companies feared at some stage to be overrun by American companies when GMO-EU policies would change. The same might happen when EU waits too long with changing policies – moving to product based will not be the solution though!
Q: More in general, what are the fields of application of the NBTs that are the most relevant for the Dutch/ European situation? Specific examples? And are there alternative routes to reach the same goals without the use of NBTs? What would be the consequences of the alternative routes?	
P1	Kansen: domesticatie van nieuwe gewassen. Zouden we dit opmerken in Europa? Als voorbeeld: Verwante soort bijv de groundcherry die snel is gedomesticeerd – onderscheid zal heel lastig zijn – zal apart onderzoeksproject zijn.
P2	*niet behandeld, buiten de expertise*
P3	Niet specifiek behandeld
P4	Niet specifiek behandeld

P5	Zie boven
P6	That depends completely on regulation and on consumer and retail acceptance. First products will need to have very clear consumer of environmental benefits. Of course the same will be reached conventionally, but too slow to sufficiently contribute to the Green deal. Sierteelt benut sowieso mutatieveredeling om 'ballast' die door kruising zou ontstaan te mijden. Deze sector zou GMOs mijden omdat dit voor dergelijke kleine gewassen niet haalbaar is. Sierteelt is ook de focus van gespecialiseerde bedrijven zoals Hudson River Biotechnologies
Extra Q BDRJFSLEVEN - Consumenten en publieke perceptie: Welke invloed heeft dit op het werk met GGO's? Verschillen nieuwe technieken hierin van oudere technieken?	
P4	<ul style="list-style-type: none"> <li>Expert noemt verder dat een breed draagvlak voor de techniek (NBT) belangrijk is en een dialoog met de samenleving aan moet worden gegaan. <ul style="list-style-type: none"> <li>Mensen willen graag weten waar hun eten vandaan komt en hoe dit geproduceerd is.</li> <li>Noemt voorbeeld: o 'hoe kun je nou een plant maken uit een celcultuur',</li> <li>Klant meenemen in proces van productie, creëren van awareness wat is het biologische verschil met een gewone plant?</li> </ul> </li> <li>noemt positieve imago groentensector, heeft dit impact op het handelen van de firma?</li> <li>heeft te maken met ontwikkelingen in de sector, dit zijn meestal kleine (familie)bedrijven, alhoewel er ook steeds meer grotere spelers komen. Deze bedrijven hebben een andere positie in de maatschappelijke discussie (dan bijvoorbeeld de grote bedrijven achter de grote GM landbouwgewassen), een positief imago maar ook verantwoordelijkheden. o In groente moet je ook met veel meer factoren rekening houden, andere scope en focus op andere events dan de grote landbouwgewassen. Juist focus op bijvoorbeeld inkruisen van ziekteresistenties. o 'Multi-edited' traits zul je niet zo snel in groenten aanbrengen maar wellicht wel in bijvoorbeeld soja</li> </ul>
P5	<ul style="list-style-type: none"> <li>De GMO discussie is ontspoord</li> <li>Voorbeeld: tolerant sojabonen zijn afgezet, maar men heeft de consument nooit verteld wat de voordelen waren</li> <li>communicatie is belangrijk</li> </ul>
P6	Niet specifiek behandeld

### A3.1.5 Regulatory Aspects

Q: When looking at the international perspective, what are your main concerns related to the upcoming application of NBTs in plant breeding? What do you see as the major issues in this respect? Specific examples?	
P1	Niet specifiek behandeld
P2	<p>Het kan een vooruitgang kan zijn als we product-gebaseerd en science-based gaan werken, maar het ligt er wel aan hoe de regelgeving eruit gaat zien. Product-gebaseerd kan ook een hele zware en moeilijke veiligheidsbeoordeling geven. Bijv. Met metabolieten, als ieder nieuw metaboliet uitgebreid getest moet worden, is het alsnog heel veel werk. Men kan er in doorslaan, in veiligheidsbeoordeling – zoals nu met transgene planten. Die valkuil is er nog steeds. Om dat te voorkomen: mensen die zorgen hebben over GM-technieken, kies dat wat met 'biologische' labeling beschikbaar is. Honoreer deze zorgen van mensen- zodat voor andere mensen die NBTs wel aanvaardbaar vinden producten met nieuwe technieken wel beschikbaar zijn. Zorg vooral voor een proportionele beoordeling! (Science-based is niet noodzakelijkerwijs proportioneel !)</p> <p>Hoe zou je dat ingevuld willen zien?</p> <p>P2: De klassieke veredeling, gaat tot nog toe goed, ook al zit er geen veiligheidsbeoordeling in - dat geeft vertrouwen dat plantenveredelingssector veilige producten kan leveren zonder strenge beoordeling. Ik ben huiverig voor onnodige beoordelingen, die voortgang remmen, en zo de taak om de wereld van voedsel te voorzien bemoeilijken.</p>
P3	In de rest van de wereld, zelfs in Rusland wordt veel in gene-editing geïnvesteerd. Ze vinden het waarschijnlijk prima dat in de EU niets gebeurt, andere landen willen graag hiervan profiteren.
P4	Niet specifiek behandeld
P5	<ul style="list-style-type: none"> <li>De huidige regelgeving is te kostbaar. Ook als men nieuwe gentechieken bij grote gewassen gaat gebruiken zal het moeilijk zijn door de huidige regelgeving <ul style="list-style-type: none"> <li>We moeten oppassen dat er niet monopolie ontstaat door de huidige regelgeving</li> <li>De grootste hurdle is de toelating, zelfs voor grote bedrijven.</li> <li>Als gevolg van de regelgeving komt de nieuwe technologie in handen van een handjevol bedrijven.</li> <li>De technologie moet ook toegankelijk worden voor kleine bedrijven</li> </ul> </li> </ul>
P6	NBT are cheaper to deal with – not traceable, so different from transgenes. Currently developers are proud and publish in scientific journals. That is likely to change soon.

<i>Q: Do you believe that harmonisation of regulatory requirements is important in this respect? Specific examples to underpin your conviction?</i>	
P1	Niet specifiek behandeld
P2	<p>■ bijv. via UPOV</p> <p>P2: Mogelijk. Veiligheid moet niet verwaarloosd worden, maar er is grote kans op doorschieten in beoordeling. Zorg dat veredelaar verantwoordelijk is bij het op de markt brengen van een onveilig product. Maker van het ras verantwoordelijk (producent) voor het probleem. Dan zal de veredelaar zelf heel kritisch kijken naar veiligheid en 'unintended' effects, en is een zeer uitgebreide veiligheidsbeoordeling door de overheid niet nodig.</p>
P3	Niet specifiek behandeld
P4	<p>■ noemt Franse situatie; P4 o is een proces-product discussie; expert volgt de Franse situatie uit interesse § Wat wil Franse overheid? Focus op techniek? Onrust in samenleving over NBTs/GMOs o In groente geen voorbeelden van in vitro mutagenese bekend ■ zou product-gebaseerde regelgeving ook als 'boemerang' voor de firma uitpakken? · Expert: het wordt eenvoudiger met product-based regelgeving, dit is interessant mits er goede harmonisatie is. Zonder goede harmonisatie kom je in de problemen als je bijvoorbeeld gaat exporteren naar een land met een streng GMO regime.</p>
P5	Niet specifiek behandeld
P6	Very much – genetic resources are global and since edits are not traceable, breeders will use them knowingly or unknowingly
<i>Q: What would be your preferred route of harmonising regulatory requirements? Who should take the initiative to come to harmonised requirements? Would you be willing to participate in meetings on harmonisation (should these be organised at some stage)?</i>	
P1	Niet specifiek behandeld
P2	Niet specifiek behandeld
P3	In de rest van de wereld, zelfs in Rusland wordt veel in gene-editing geïnvesteerd. Ze vinden het waarschijnlijk prima dat in de EU niets gebeurt, andere landen willen graag hiervan profiteren.
P4	Niet specifiek behandeld
P5	Niet specifiek behandeld
P6	Internationale harmonisatie: had 5 jaar geleden gemoeten, samen met landen als Australië, Japan, etc. Nu is het ontzettend moeilijk om nog internationaal te harmoniseren. This questions should have been asked some 5 years ago or earlier. Trying to harmonise in the Cartagena Protocol is a dead-end street because of the dominance of NGOs in the CBD. It needs to be done among progressive states (Japan, Australia, Argentina and possibly USA) and EU. If EU is serious it can only enter such discussions when they realise they cannot be the dominant party. EU is only in a position to follow rather than lead in this area
<i>Extra Q bedrijfsleven: Welke invloed heeft dit op het werk met GGO's? Verschillen nieuwe technieken hierin van oudere technieken?</i>	
P4	<p>· Expert noemt verder dat een breed draagvlak voor de techniek (NBT) belangrijk is en een dialoog met de samenleving aan moet worden gegaan. o Mensen willen graag weten waar hun eten vandaan komt en hoe dit geproduceerd is. o Noemt voorbeeld: o 'hoe kun je nou een plant maken uit een celcultuur', wat is het biologische verschil met een gewone plant? o Klant meenemen in proces van productie, creëren van awareness</p>
P5	Niet specifiek behandeld
P6	Niet specifiek behandeld
<i>Additional discussed topics</i>	
P2	<p>p2: Ik pleit voor een onderscheid tussen veiligheidsbeoordeling en labeling. Dit onderscheid wordt nu niet of niet voldoende gemaakt. De GMO regelgeving vraagt om een uitgebreide risicobeoordeling, zelfs al is er weinig of niets veranderd aan een product. Mensen kunnen toch tegen een GMO (of product gemaakt met CRISPR-CAS) zijn: er zijn mensen die vanwege hun grondhouding (of levensbeschouwing) technieken afwijzen, en dat dient gerespecteerd te worden. Door juiste labeling kan men zelf kiezen of men producten met nieuwe technieken koopt – er moet keuzevrijheid voor zijn. Goede labeling is daarvoor voldoende, labels als biologisch of dynamisch (bijv.). Veiligheidsbeoordeling moet niet heel streng worden omdat er mensen zijn die vanuit hun grondhoudinglevensbeschouwing technieken afwijzen. Maak duidelijk onderscheid: tussen regelgeving voor veiligheid, en regelgeving voor labeling. ■ Dus, jouw visie is proces-gebaseerde insteek voor veiligheid loslaten, maar product-gerelateerd voor veiligheid. Wat betreft labeling: wel proces-gebaseerd, net zoals bij biologisch, een 'positief' keurmerk. P2: qua keurmerk is het vergelijkbaar met de situatie voor kunstmest: het gebruik hiervan zie je niet in het eindproduct, maar is wel belangrijk voor het label ■ hoe zit het met puntmutaties in dit geval: P2: Als een puntmutatie van nature ontstaat dan kan een label als 'biologisch' i.i.d. gebruikt worden. Als (dezelfde) puntmutatie met technologie (bijv CRISPR-Cas) is aangebracht, dan het label 'biologisch' niet gebruiken. Toevoeging achteraf: Een GMO label is passend bij transgene producten. Dat is al voorgeschreven, en kunnen we zo handhaven. Als er een GM-techniek is gebruikt tijdens het proces maar het product geen vreemd DNA bevat, vind ik het niet verstandig een GMO label te gebruiken. Vanwege het gebruik van de techniek, zal het positieve label 'biologisch' o.i.d. niet gebruikt moeten worden. Zo houden consumenten</p>



	die geen producten willen waarbij een GM-techniek is gebruikt tijdens het proces toch keuzevrijheid. Zo ontstaan er drie groepen producten: 1. Transgene producten -> GMO label; 2. Producten waarbij geen GM technieken zijn gebruikt -> Label 'biologisch' 3. Producten waarbij wel GM technieken zijn gebruikt maar die geen soortsvreemd DNA bevatten -> Geen label.	
P3	De EFSA geeft advies over een GMO event, EFSA zegt niet of iets gelabeld moet worden. In EU wordt geen GMO voor humane consumptie gebruikt, dus wordt niet gelabeld. Stel dat wij zouden zeggen dat alles wat het milieu schade toebrengt moet worden gelabeld, dan zou zo ongeveer alles gelabeld moeten worden, veel producten die wij dagelijks gebruiken schaden het milieu (onafhankelijk van GMO). We gebruiken dagelijks producten die dit doen.	
P4	noemt het inzetten van gene-editing voor onderzoeksdoeleinden - argument. Graag gene-editing gebruiken voor onderzoek omdat je dan specifieke mutaties kan maken i.p.v. afhankelijk te zijn van random mutaties - dit heeft duidelijke voordelen, en is bijvoorbeeld ook nauwkeuriger voor allelen.	Expert: dat is ook ons
P4	dit is dan meer ingeperkt gebruik, kan met de huidige regelgeving. de voeten voor ingeperkt gebruik met de huidige GMO regelgeving, voldoende ruimte voor onderzoek. Hiervoor zou een aanpassing van de regelgeving niet veel uitmaken, dat is juist meer voor commerciële toepassing.	Expert: wij kunnen prima uit
P4	noemt positieve imago groentensector, heeft dit impact op het handelen van de firma? o heeft te maken met ontwikkelingen in de sector, dit zijn meestal kleine (familie)bedrijven, alhoewel er ook steeds meer grotere spelers komen. Deze bedrijven hebben een andere positie in de maatschappelijke discussie (dan bijvoorbeeld de grote bedrijven achter de grote GM landbouwgewassen), een positief imago maar ook verantwoordelijkheden. o In groente moet je ook met veel meer factoren rekening houden, andere scope en focus op andere events dan de grote landbouwgewassen. Juist focus op bijvoorbeeld inkruisen van ziekteresistenties. o 'Multi-edited' traits zul je niet zo snel in groenten aanbrenge maar wellicht wel in bijvoorbeeld soja	

## A3.2 Animal Sector Interviews

### A3.2.1 Developments

	<i>Q: What do you consider as the most important developments in animal breeding? Specific examples?</i>	
A1	<p>A1: Binnen gentechniek, niet zo heel veel ontwikkelingen. Het belangrijkste zijn de grote fokprogramma's. Binnen vaccin ontwikkeling, viraal, bacteriaal, zie je wel veel voorbeelden van gentechniek. Gentech bij dieren is nog niet relevant. Juridisch is het ook nog lastig. Sinds Dolly het schaap, vorige eeuw, is er eigenlijk niet veel gebeurd</p> <p> : Een hoornloos rund is ontwikkeld met gene editing, in Brazilië</p> <p>A1: De vraag is hoe gene editing zich verhoudt tot fokprogramma's. Er zijn geen ontwikkelingen in gene editing voor 'bij de boer' (voor zover bekend). Er zijn wel voorbeelden van kippenlijnen waar gene editing is toegepast, bijvoorbeeld voor het creëren fluorescente macrofagen om deze te kunnen traceren, maar dit is voor experimenteel onderzoek.</p> <p> bij varkens wordt wel onderzoek gedaan naar varkenspest resistentie</p> <p>A1: er is nu wel veel onderzoek naar PRRSV, maar met name met fokprogramma's. (SNP's)</p> <p> : bij de hoornloze runderen is per ongeluk een plasmide geïntroduceerd bij het gene editing Daarom zijn de dieren eigenlijk GMO Nu door naar de volgende vraag</p>	
A2	<ul style="list-style-type: none"> <li>• genomic selection; je kunt preciezer en efficiënter fokken</li> <li>• de metingen worden goedkoper; bijvoorbeeld om de gezondheid van de dieren te monitoren</li> </ul> <p>A2 vertelt: de afgelopen 20 jaar: als het gaat om genetische modificatie van landbouwhuisdieren, dan is er veel gebeurd. Maar er zijn geen nieuwe gecertificeerde rassen gemaakt. De fokkerij werken ahv de vraag van de boeren. Als je gene editing gaat gebruiken, dan kun je variatie creëren A2 praten over voorbeeld hoornloze koeien. Hoornloze dieren kun je ook op een andere manier (noemt het 'de goede manier') creëren, maar moeten de vraag stellen 'wat betekent dit voor de genetische diversiteit'? De genetische diversiteit wordt behouden in genenbanken voor de toekomst.</p>	
A3	<p>Genomic prediction tot op sequence niveau, genotyperen van 100.000en dieren. Deze kennis nodig om te komen tot GMOs, en targets tot gene editing.</p> <p>Alles wordt steeds meer geautomatiseerd, steeds grotere bedrijven die het grootste deel van de markt in handen hebben. Grootschalige industriële productie met steeds preciezere technologie.</p>	

A4	<ul style="list-style-type: none"> <li>• Het toepassen quantitative genetics</li> <li>• Mbv veredelingsprogramma's: het benutten van natuurlijke variatie die aanwezig is</li> <li>• De ontwikkelingen op het terrein van sensoren</li> <li>• Genomic selection; genotypes meten op DNA niveau, bestaat nu al zo'n 10-15 jaar</li> <li>• Het verkrijgen van informatie over anonieme SNPs in het genoom</li> <li>• Genome-editing toepassing in veredeling in fundamenteel onderzoek: het achterhalen van de functie van genen. En deze kennis van genen zou men in veredelingsprogramma's kunnen gebruiken</li> <li>• Op welke kenmerken moet men focussen? <ul style="list-style-type: none"> <li>o [redacted] is het produceren van gezonde melk ook een voorbeeld? (dus aanpassen van bijvoorbeeld vetten in melk) [redacted] uit onderzoek kwam er geen helder beeld naar voren wat er nu gezond is. Niet duidelijk welk gen er veranderd moet worden om gezondere melk te produceren.</li> <li>o [redacted] vooral de focus op gezondheids- en welzijnskenmerken.</li> <li>o noemt SLICK als voorbeeld; dieren die veel beter met hitte overweg kunnen, en POLLED: hoornloze runderen. Deze kenmerken komen ook van nature voor, kan met gene-editen versneld worden ingevoerd in populaties.</li> <li>o noemt ook resistentie voor ziekten. Kanttekening: het gaat er vooral om dat virusverspreiding niet plaats vindt. Het is een nachtmerrie als de dieren niet meer ziek worden maar het wel verspreiden. Een voorbeeld: eenden zijn resistent tegen vogelgriep maar zijn wel drager. Zorgen om trekvogels omdat vogelgriep wordt verspreid. Dus, beide processen moet je aanpassen.</li> <li>o African swine fever voorbeeld. De uitdaging hierbij is het juiste gen te vinden. De meeste eigenschappen worden niet door 1 gen bepaald.</li> </ul> </li> <li>• Genetische modificatie mogelijk. Het is bewezen met stier Herman <ul style="list-style-type: none"> <li>o De GM technologie was wetenschappelijk leuk en interessant, maar het was geen optie voor de fokkerij. Er is geen vegetatieve vermeerdering bij dieren, in tegenstelling tot bij planten. Je moet een populatie dieren hebben; met de oude GM technieken is dat niet mogelijk.</li> <li>o Dit is heel anders voor genome editing. Genome-editing kan rol spelen in veredeling, vooral voor kenmerken waarbij nu de hulpmiddelen ontbreken. Noemt het introduceren van genetische variatie</li> </ul> </li> </ul>
A5	<p>De veehouderij werkt heel anders dan plantenveredeling. Alle veredeling gebeurt binnen rassen – verwacht dat dat blijft. Belangrijkste verandering fokkerijorganisatie is de professionalisering van de sector: van sector met kleine spelers naar een sector met grotere spelers die steeds kennisintensiever werken. Genus Plc. marktleider: varkens, kip, runderen, investeert ook fors in gene editing, bijvoorbeeld in het ontwikkelen van een varken resistent tegen respiratoire ziekte PRRS. Andere technische ontwikkelingen die van belang zijn: Ontwikkeling van Spermasorteertechnieken en ontwikkelingen in het werken met embryo's (direct verkopen, gekruiste embryo's). Sector wil lering trekken uit plantensector. Binnen de veehouderij zijn oplossingen nodig voor vraagstukken omtrent klimaat, methaan, antibiotica resistentie, niet voor hogere opbrengsten.</p>
A6	<ul style="list-style-type: none"> <li>• Genomics bij veredeling/fokken van koeien. Sinds 2008 commercieel en toepassing bij koeien wereldwijd. 90% van koeien die Altagenetics verkoopt is gebaseerd op genomics. De gezondheid van de koe, met name de klauwgezondheid, is cruciaal. De database wordt steeds groter. A6 noemt dat de melkveehouderij in Nederland nog heel traditioneel is. Maar er is een tweedeling zichtbaar; veredelaar en commerciële tak (met de focus op een goed product met zo min mogelijk gedoe).</li> </ul>
Q: What do you see as the most beneficial developments? Specific examples?	
A1	<p>A1: de grote vraag hier is, wat is beneficial? Dat is lastig te beantwoorden. In sommige gevallen is het misschien beter om het systeem en/of de manier van houden aan te passen, in plaats van de dieren zelf. Nu heb je bijvoorbeeld dat staarten van varkens geknipt worden, of dat kippensnavels gekapt moeten worden. Mogelijk zou je door te fokken, al dan niet met dieren met gene edits, deze problemen kunnen verminderen of verhelpen, maar deze problemen zijn het gevolg van de huisvesting. Ook voor ziekte resistentie is het vergelijkbaar, voor een deel is de huidige huisvesting een risico voor ziekteverspreiding.</p> <p>Daarnaast is het zo dat als je genen modificeert om ziekte resistentie te veranderen, je mogelijk ook andere, negatieve, effecten kunt veroorzaken.</p> <p>[redacted]: Klopt, dat lijkt nu ook het geval bij de kinderen in China, die door de gene edit die AIDS risico moest voorkomen, mogelijk juist vatbaarder zijn voor andere ziektes</p> <p>A1: In de veehouderij zou gene edits kunnen toepassen die productiekenmerken beïnvloeden, maar de vraag is of men dat moet willen. Het is hier heel lastig te bepalen wat 'beneficial' is: voor wie of wat is het beneficial, en welke bijwerkingen zijn er mogelijk? Er zijn wel veel situaties waarbij gene editen een oplossing zou kunnen zijn, binnen de huidige omstandigheden.</p> <p>[redacted]: Ook in het huidige doorfokken wordt geselecteerd op bepaalde productiekenmerken</p> <p>[redacted] Inderdaad, ook in de normale fok vindt dat plaats. Met gene editen zou dit ook kunnen, mogelijk versneld.</p> <p>[redacted] Veel traits relevant voor de veehouderij zijn polygeen, kun je daar iets over zeggen</p> <p>A1: Idd, er zijn polygene traits, en phenotypes zijn complex. Dit heeft een biologische reden: één fout(je) in het DNA leidt niet gelijk tot catastrofale gevolgen. Soms is er sprake van synergie tussen bepaalde traits, soms is er juist sprake van trade offs. Dit maakt het lastig om polygene traits te wijzigen. Situaties waar ik me kan voorstellen waar edits voordelig kunnen zijn, zijn oa: gene edits om reproductie van vissen in kweeksystemen te</p>



	verbeteren. Misschien zijn er ook mogelijkheden om bij pluimvee (mn kippen) te editen voor sexen. Vanuit de maatschappij moet bekeken worden wat als 'beneficial' kan worden beschouwd.
A2	<ul style="list-style-type: none"> <li>• Wat betreft gene editing, genetische veranderingen die het publiek waarschijnlijk beter zal accepteren zoals resistentie tegen virus bewerkstelligen, dierenwelzijn bevorderen of goed voor het klimaat zijn (noemt hier de Enviropig als voorbeeld; geen stikstof uitstoot).</li> </ul> <p>A2 vertelt: in het algemeen is er een toenemende weerstand tegen de fokkerij. Gene editing doet er een stapje bovenop [ ] zegt dat het publiek tijd nodig heeft voor acceptatie. De fokkerij heeft ook een negatief imago onder de wetenschappers.</p>
A3	<p>Als bedrijf steeds meer richten op grote bedrijven, want daar is veel winst te halen.</p> <p>Meer persoonlijk een zorgelijke ontwikkeling: in grote systemen verdwijnt de individuele aandacht voor het dier (mega-stallen).</p> <p>Gevoelens zijn beter als de eigenaar de dieren iedere dag ziet (kleinschalig), ook al zitten de dieren onder slechte omstandigheden. Gaat vaak om perceptie.</p>
A4	Zie boven
A5	Niet specifiek gevraagd, zie boven
A6	• Vraag niet behandeld.
<i>Q: What do you see as developments of concern? Specific examples?</i>	
A1	<i>*Niet specifiek gevraagd, wel deels aan bod gekomen binnen voorgaande vraag</i>
A2	<ul style="list-style-type: none"> <li>• de langer termijn risico's: de versmalling van de genetische basis; zou ten koste kunnen gaan van de genetische diversiteit. Noemt als voorbeeld de AquaBounty zalm; als dit product op de markt zal blijven zal er geen andere zalm meer veredeld worden.</li> <li>• de macht die de grote spelers op de markt zullen krijgen. Noemt als voorbeeld: er zijn meer twee bedrijven in de wereld die kippen(rassen) op de markt zetten. Met de nieuwe technieken zouden grote spelers de marktpositie kunnen veroveren en de kleine spelers buiten spel zetten.</li> </ul>
A3	zie vraag hierboven
A4	<ul style="list-style-type: none"> <li>• als we kijken naar klassieke veredeling dan weten we dat er trade-offs zijn als je teveel nadruk legt op 1 kenmerk, bijvoorbeeld de groei. Het vraagt om een gebalanceerde vooruitgang, gericht op het totale dier omdat we een zeer beperkte kennis hebben over het genoom en de biologie die een rol speelt. Daarom: zorgvuldig monitoren populatie. Bij HG hebben ze uitvoerige testprogramma's.</li> <li>• Nu: geen verantwoordelijke toepassing van GM technologie. Het voorbeeld van de Aquabounty zalm wordt genoemd. <ul style="list-style-type: none"> <li>o Het is een lastige casus. Het is als succesvol gepresenteerd, maar dat is lareikoek. Het heeft 12 jaar geduurd voordat het op de markt kwam. Je moet altijd een vergelijking maken; Aquabounty zalm groeit niet harder dan andere zalmen op de markt. Voor dit specifieke kenmerk (groei) hebben we de GM technologieën niet nodig. Het is lastig om ruimte te krijgen voor de toepassing van GM technologieën door dit voorbeeld. Het is door Canada op de markt gedumpt en een bedreiging voor de overige zalm op de markt (verkregen door traditionele selectie) omdat de consument niet weet waar het vandaan komt.</li> </ul> </li> </ul>
A5	Niet direct zorgen – ik sta positief tegenover technologische ontwikkelingen. Gene editing nog heel erg in de onderzoeksfase voor veehouderij. Er moet opgepast worden met de claim dat gene editing volledig onder controle is en met zeggen dat gene editing hetzelfde is als fokkerij (qua risico's en veiligheid). Deze claim is te makkelijke gedachtegang – Het is nog te vroeg om gene editing gelijk te stellen aan fokkerij, dat is nog niet bekend
A6	<ul style="list-style-type: none"> <li>• Zijn grootste zorg is dat er geen geld wordt verdiend. A6 noemt het voorbeeld van het aantal dieren dat een boer moet hebben voor een fatsoenlijk inkomen (bijvoorbeeld, voor een kippenboer zijn dit 400.000 kippen en voor een melkboer zijn dit 250 koeien). De economie is belangrijk, want alles heeft een prijs. Er is een ratrace gaande van groot, groter, grootst. Als voorbeeld noemt hij de grootste klant; deze heeft 5000 koeien (oprichter booking.com).</li> <li>• Men kan zich onderscheiden dmv genomic selection. Daarmee kun je het dierenwelzijn verbeteren. Dit moet vanuit de intrinsieke motivatie van de boer komen.</li> </ul>
<i>Q: What do you see as a realistic timeline for: CRISPR-Cas / gene edited animal products moving to the European market based on base editing?</i>	
A1	<p>A1: dat zou heel erg van de juridische aspecten afhangen. Maakt vergelijking naar plantenveredeling: mag niet met CRISPR in de EU. In de fokkerij verwacht ik dat ge-gene-edited dieren verder snel naar de markt zou gaan, omdat gene editen makkelijker en sneller kan zijn dan normale fokprogramma's. Ook binnen de farma zal het marketten van producten van gene-edited dieren snel volgen, bijv. voor vaccin productie. De ethische discussie moet dan wel gevoerd worden: wat mag wel, en wat mag niet..</p> <p>[ ] Voor gene-edited dieren is het de vraag hoeveel 'start' dieren er nodig zijn voor een gene edit om in de populatie te komen Kun je daar iets over zeggen?</p> <p>A1: Als er te weinig genetische diversiteit is bij dieren, kan dit bezwaarlijk worden: gevoeligheid voor ziektes, voor klimaatwisselingen. Dit probleem is hetzelfde voor normale fokkerij.</p> <p>[ ] Off target effecten kunnen mogelijk ook problemen geven, hoe verhoudt zich dit tot de diversiteit</p>

	A1: Erfelijkheid van traits speelt hier ook een rol. Ik weet eigenlijk niet precies hoe dat zit met gene edits, en of en hoe die overerven.
A2	A2 zou er niets over kunnen zeggen. Dit zal afhangen van vermenigvuldigings- en reproductietechnieken. Dit is commercieel erg belangrijk en soms zelfs cruciaal. Dit is per diersoort verschillend; een voorbeeld tijdens dit proces is het invriezen van embryo's van varkens (moeilijk) t.o.v. runderen (makkelijk). Een tip van A2 is om met een reproductie-expert te praten.
A3	Verwacht dat er wel iets op de Europese markt zal komen in 5-10 jaar, op wereldmarkt wellicht al sneller (3-5 jaar), in geval van dieren.
A4	<p>• Als we regelgeving buiten beschouwing laten dan is het produceren/editen niet het probleem. Het kan. • De uitdaging is, welk gen wil je editen? Dat is niet groei of het aantal eieren. Dat zijn de welzijn- en gezondheidstargets</p> <p>o Noemt als voorbeeld de betrokkenheid bij project dat gaat over de castratie bij varkens (Recombinetics samenwerking). Er kan genetisch ervoor gezorgd worden dat varkens niet in de puberteit komen. Mannelijke dieren (beren) worden niet seksueel volwassen en vertonen geen berengeur (dat is geen prettige geur, off-flavour). In de huidige situatie worden varkens gecastreerd.</p> <p>o Noemt het proces en de tijd die nodig is voor elke stap. Vanaf de start tot het bij de klant hebben duurt in totaal +/- 12 jaar. Het vaststellen of de edit een gewenst effect heeft is eenvoudig. Het niet geslachttrijp worden is meetbaar. Maar, de kennis over het genoom is beperkt en de ongewenste eigenschappen zijn onbekend, bijvoorbeeld waar is het gen nog meer bij betrokken? Dus als men ongewenste eigenschappen tegenkomt tijdens het proces, dan moet men terug naar de tekentafel.</p> <p>o Edit -duurt 4 jaar, implementeren – duurt 4 jaar, op de markt, duurt ook nog 4 jaar.</p>
A5	Als het toegestaan is, dan gaat dat wel komen PRRS tolerant varken zal dan komen. Bij runderen geldt: 'no genes, no editing', er zijn nog weinig genen bekend die een relevant verschil maken. Onthoornen: eerste voorbeeld waar wel opties zijn. Zal echt nog wel 10 jaar duren voordat het op de markt komt. Vrijheid om gene editing in te zetten als onderzoekstool vind ik heel belangrijk. Dit wordt in Europa nauwelijks toegestaan, terwijl wereldwijd juist ervaring opgedaan wordt met gene editing. Wij doen nu een samenwerking Oceanië, in overheidsproject over gene editing als eerste verkenningen. Bottleneck in de veehouderij bij het gebruik van gene editing: reproductietechnologie! De verspreiding van een edit in de populatie is nodig – werkt heel anders dan bij planten. Reproductietechnologie blijft nodig in veehouderij. Daar spelen ethisch dilemma's ook (bijv. bij embryo's kloneren of andere embryotechnologie). Ik sprak laatst nog met een collega over het feit dat in vitro embryobehandeling ook risico's met zich mee kunnen brengen.
A6	<p>• AB6 denkt van niet. En zo wel, dan zou het vlees van gene edited dieren een 'guilty pleasure' worden. Als men het gebruikt om de gezondheid van het dier te verbeteren dan zou het kunnen, maar niet voor de verhoging van de vleesproductie. Het dierenwelzijn is hierbij belangrijk, want dieren hebben ook gevoel. Hij noemt de Belgian blue als voorbeeld. Ingrijpen bij bevalling kalfje; onprettig voor dier en daarbij zijn de kosten van de boer hoger voor elk kalfje.</p>
<i>CRISPR-Cas / gene-edited animal products moving to the European market based on HDR procedures?</i>	
A1	<i>*Niet specifiek behandeld*</i>
A2	<i>*Niet specifiek behandeld*</i>
A3	Met grote veranderingen zal het nog wel iets langer duren.
A4	<i>*Niet specifiek behandeld*</i>
A5	<i>*Niet specifiek behandeld*</i>
A6	<i>*Niet specifiek behandeld*</i>
<i>Synthetic biology – derived animal products, with characteristics unknown to nature, moving to the European market?</i>	
A1	<i>*Niet specifiek behandeld*</i>
A2	<i>*Niet specifiek behandeld*</i>
A3	<i>*Niet specifiek behandeld*</i>
A4	<i>*Niet specifiek behandeld*</i>
A5	<i>*Niet specifiek behandeld*</i>
A6	<i>*Niet specifiek behandeld*</i>
<i>Q: What do you see as major issues when comparing the current basically process-based regulations versus an alternative product-based regulations?</i>	
A1	<i>*Niet specifiek gevraagd*</i>
A2	A2 zei na de uitleg van [REDACTED] op het eerste gezicht, een product-based benadering. Zou er meer over kunnen zeggen als A2 er meer over zou weten (doelt op beide benaderingen).
A3	<i>*Niet specifiek behandeld*</i>
A4	<i>*Niet specifiek behandeld*</i>
A5	Definitie veilig product is onontgonnen in ons gebied – is lastig. Referenties zijn nodig, dat is niet opgebouwd in de veehouderij. In de sector is men niet mee bezig om aan te tonen dat iets veilig is (in tegenstelling tot de

plantsector) Het gedrag van dieren moet ook vergeleken worden bij edits. We werken samen in een project met Wageningen Livestock Research over veredeling bij dieren in het algemeen, met vragen als: hoe ver mag je gaan met een dier veranderen? Wat is goed en niet goed, wat is wel en niet natuurlijk? Gene editing, next level qua technologie – je kan er veel mee aanpassen, maar bovenstaande ethische vragen spelen evengoed.

A6 · Deze vraag kan A6 niet beantwoorden, dat weet hij zo niet

### A3.2.2 Traceability

A1 A1: De beslissing van het EJC is meer een maatschappelijke. Gene editing is maatschappelijk onbekend, en dat betekent onbemand. Er hangt een soort science fiction idee omheen. Toch zijn er, volgens mij bij rijst producten, al veel gemodificeerde rassen op de markt.

In het huidige tijdperk, waar social media een grote rol speelt, kunnen berichten zich heel snel verspreiden. Dus ontwikkelaars moeten goed nadenken op product niveau hoe ze hun product moeten benoemen – negatieve publicatie kan namelijk heel hard gaan.

Als we goed nadenken kunnen we veilige producten maken met gene editing. De techniek zelf is niet gevaarlijk voor voedselproducten, het DNA blijft hetzelfde – en nu eten we natuurlijk ook DNA.

Binnen de veehouderij kan Gene-edited zorgen voor een versneld breeding programma, dat hoeft geen gevaar op te leveren.

5.1.2 De beslissing van het ECJ is inderdaad meer politiek, niet zo zeer over de veiligheid Vandaar ook dat we nu kijken naar een meer product-georiënteerde aanpak, waarbij nieuwe producten geëvalueerd moeten worden

A1: Het is verstandig om aan de voorkant te zorgen dat een product mogelijk en veilig is, vóórdat de ontwikkeling plaatsvindt. De vraag is wie in de commissie kan plaatsvinden die over aanvragen mag oordelen. En de vraag blijft: wanneer is een modificatie beneficial?

We moeten niet alle gene editing toepassingen en mogelijkheden over een kam scheren. Embryo editing voor oogkleur, lengte of andere uiterlijke kenmerken is iets anders dan ziektes voorkomen. Het hangt allemaal af van de toepassing.

Modificaties zoals minder eten, maar meer groeien zijn voor de veehouderij wel gewenst, mogelijk ook om een carbon foodprint te verkleinen. Maatschappelijk ligt dat complexer.

Hoe het maatschappelijk debat op dat moment loopt, bepaalt waarschijnlijk ook de acceptatie. Bijvoorbeeld, met de huidige stikstofproblematiek zou de interesse voor modificaties die leiden tot minder stikstof uitstoot bij koeien - minder uitstoot of fixatie - misschien wel instemming vinden.

: Toch nog even naar de traceability, zie je mogelijkheden om met sequencing of met event-specifieke methoden producten te kunnen traceren

A1: Modificaties die tot single nucleotide veranderingen hebben geleid, kun je niet traceren – die variatie is normaal gesproken ook aanwezig.

Of er andere manieren van traceability zijn, weet ik niet zo goed. Als je een tracer zou inbouwen in het DNA, krijg je juist veranderingen die je niet wil. Of als je met synthetische nucleotiden wilt werken.

voor de handhaving van de wettelijke regels is traceerbaarheid van belang – vandaar dat we deze vragen in het interview erbij hebben

A2 Bijna onmogelijk, voor zowel planten, micro-organismen en dieren. Certificerings-achtige manier van denken; niet op het product focussen maar op het proces.

A3 Is makkelijk uit te voeren, als een kleine mutatie ook kan. In startfase aantrekkelijk, je weet dan beter wat er gebeurt en kan gevolgen traceren.  
Gene edits zie ik als inbrengen van SNPs, bij GMOs het inbrengen van grote stukken. In fokkerij heb je vaak juist veel SNPs door natuurlijke variatie.  
Ter illustratie - als referentie wordt vaak een Tabasco varken gebruikt; een ander dier zal veel indels hebben ten opzichte van dit referentie en vice versa.  
Gebruik van lijnspecifieke genomen sequenties neemt toe, maar single SNPs detecteren blijft lastig ook door natuurlijke variatie, GMOs detecteren is makkelijker door de grotere genetische aanpassing.

-Ziet u mogelijkheden om dieren met meerdere edits te traceren?

\*\*Niet behandeld\*\*

-Ziet u mogelijkheden om bepaalde 'traits' (/eigenschappen) te traceren? Zo ja, welke bottlenecks voor traceren van traits zijn mogelijk een punt van zorg?

Loss & gain of function is dit in feite, beantwoord in bovenstaande vraag.

A4 · in het debat zijn er 2 typen toepassingen:

o een variant die al aanwezig is, dus een edit wat al van nature voorkomt. Hierbij wordt er geen nieuwe genomesequentie gecreëerd. Voorbeeld als SLICK en POLLED, niet vreemds inbrengen, het is niet te traceren.  
Kloneren is ook niet te traceren. Bij genome-editing kun je in de buurt van de edit iets nieuws/extra inbrengen

	(maar de marker die je ernaast zet moet men dichtbij zetten anders ben je het kwijt). Maar de vraag is, kun je garanderen dat het geen effect heeft?
	o Toevoeging nieuw stuk DNA. Daar komt de ethische discussie bij kijken; eigenschappen toevoegen, is dat wenselijk? Is het zonder consequenties voor het dier? En voor de consument?
A5	Eventspecifiek – extra uitleg <span style="background-color: yellow;">      </span> Gen ingebouwd op willekeur plek in genoom: deze sequentie is uniek. En over 'barcode systeem' express een herkenbare mutatie inbrengen' Als je base specifiek werkt: dan is dit niet te onderscheiden van natuurlijke mutatie. Je kan als je de technologie volledig onder controle hebt express iets inbouwen, een barcode systeem kan je technisch doen. Maar wil je dat? Dit is dan niet meer 'wat in de natuur voorkomt' Misschien wil je (als partij die en dier met edit op de markt brengt) wel traceerbaarheid, zodat anderen niet 'jouw edits' kunnen gebruiken <span style="background-color: yellow;">      </span> Zou u bereid zijn om barcode toe te passen? Maatschappelijke acceptatie is de vraag. Als het geaccepteerd zou zijn en veilig voor het dier(!), dan zouden we daar interesse in hebben. Voordelen dat dieren te vinden zijn, dat zou omarmt worden vanuit de sector. Maatschappelijke acceptatie is de vraag. Als het geaccepteerd zou zijn en veilig voor het dier(!), dan zouden we daar interesse in hebben. Voordelen dat dieren te vinden zijn, dat zou omarmt worden vanuit de sector. Bij runderen geldt: alleen sperma wordt geleverd, dus levert helft van het genetisch materiaal.
A6	· bij koeien is kruisen een bekend fenomeen voor een hogere opbrengst of voor gezondere dieren (bijvoorbeeld resistentie tegen een bacteriële infectie). · A6 noemt dat het aantal nakomelingen van 1 stier is maar heel beperkt is, bij varkens en kippen is dit een ander verhaal.
<i>Q: Do you see options for traceability of multi-edited animals?</i>	
A1	<i>*Niet specifiek behandeld*</i>
A2	A2 zegt: zie antwoord hierboven. Is dit wel het geval bij dieren vraag <span style="background-color: yellow;">      </span> Ja, bij dieren moet dit wel (multiple edits) omdat de meeste relevante kenmerken zijn polygeen. Dit zou ook kunnen in combinatie met genomic selection.
A3	<i>*Niet specifiek behandeld*</i>
A4	<i>*Niet specifiek behandeld*</i>
A5	· dat is wat ze bij HG doen, daar waar ze weten waar de genen zijn met een ongewenst effect. · En dringen de frequentie terug door metingen aan het DNA. Het is een belangrijke technologie in de diervereiding. · Mbv gene editen dan kun je vaststellen wat functie is van genen. Met die informatie ga je verder. Zonder gene editing.
A6	niet gevraagd nav antwoord hierboven
6	<i>*Niet specifiek behandeld*</i>
<i>Q: Do you see possibilities for the traceability of specific traits? If so, what do you see as bottlenecks for adequate tracing of traits of potential concern?</i>	
A1	<span style="background-color: yellow;">      </span> Als het niet mogelijk is om specifieke kenmerken aan te tonen, zou den er dan andere mogelijkheden zijn om gene-edited dieren te traceren? Bijvoorbeeld door uitgebreide documentatie A1: Als je wilt bijhouden met documentatie, dan ga je ervan uit dat iedereen compleet transparant is. In een deel van de veehouderij zal het zeker uitgebreid bijgehouden worden in een stamboek hoe het gaat met een edit, om te zien hoe het overerft. <span style="background-color: yellow;">      </span> Mogelijk zou het de moeite waard kunnen zijn, als een grote handelspartner dit soort data vraagt
A2	<i>*Niet specifiek behandeld*</i>
A3	<i>*Niet specifiek behandeld*</i>
A4	<i>*Niet specifiek behandeld*</i>
A5	Met sensortechniek is heel veel vast te leggen. Veiligheid voor het dier wil je volgen (veroudering, bevattelijkheid voor ziekten). Dat duurt lang voordat je die gegevens hebt en dan is het wellicht al 'te laat'. Beter vlees, andere melk, dat is makkelijk te checken in het product. In de sector wordt vooral nagedacht over verbeteringen voor de gezondheid van dieren, efficiency, en dierenwelzijn.
A6	· Ja, bijvoorbeeld A2 melk (voor lactoseintolerantie) en hoornloosheid
<i>Q: In your view, what should be the consequence of a possible product-based approach in terms of traceability, in other words, what would still be relevant for monitoring programmes?</i>	
A1	<i>*Niet specifiek behandeld*</i>
A2	<i>*Niet specifiek behandeld*</i>
A3	<i>*Niet specifiek behandeld*</i>
A4	<i>*Niet specifiek behandeld*</i>
A5	<i>*Niet specifiek behandeld*</i>
A6	<i>*Niet specifiek behandeld*</i>



### A3.2.3 Safety

Q: What do you see as the major issue(s) when considering the safety of new gene-edited animals?	
A1	<p>A1: Als dat netjes gebeurt, zijn er geen problemen. Hangt wel af van de grenzen van de wetenschappers: er kunnen 'engerds' zijn die een schaap met 5 poten willen maken. In principe is gene editing geen gevaar, maar men moet uitkijken met hoe ver je wil gaan.</p> <p>Wat betreft Off target effecten:</p> <p>A1: Edits moeten wel heel bewust gedaan worden, als je niet weet wat je doet, dan is de veiligheid sowieso niet gegarandeerd. De welzijn en veiligheid van het dier, de veiligheid als product of de veiligheid voor de omgeving. In principe is aan DNA sleutelen altijd een risico zijn. Zorgvuldige bestudering, en volgen in de tijd zijn van belang.</p> <p>met reguliere technieken kunnen ook problemen zijn</p> <p>AR1 Dan is er wel minder risico, want de 'natuur' zelf doet ook een selectie.</p> <p>: traditioneel selecteer je ook voor bepaalde genen</p> <p>A1: Bij gene editing ga je specifiek voor de modificatie van één gen, en weet je wat ermee is gebeurd. Wat dat voor effecten heeft op bijvoorbeeld non-coding DNA of transcriptie en translatie, is nog niet zeker. Hier zijn nog wel veel wetenschappelijke vragen.</p>
A2	<ul style="list-style-type: none"> <li>• de off-target effecten die op langer termijn effecten kunnen hebben</li> <li>• groter effect veiligheid dieren dan voor mensen</li> </ul>
A3	<p>Wordt de voedselveiligheid nu meegenomen in de ontwikkeling van nieuwe rassen/lijnen? Nee, omdat we daar geen gereedschap voor hebben, wel wordt gekeken naar gedrag van dier en milieubelasting. Ook wordt gekeken naar ziektes, antibioticaresistentie.</p> <p>Ook robustness, resilience wordt meegenomen, bijvoorbeeld tegen specifieke belangrijke ziekten. Bijvoorbeeld E.coli resiliënt rassen, is alleen wel ook recessieve eigenschap, in alle drie lijnen moeten homozygoot het gen ontbreken.</p> <p>Voedselveiligheid grotendeels een gevolg van handelen in de stal en productiehygiëne, bijv. selectie toelating op bedrijven. Wat zijn wat u betreft belangrijke aandachtspunten voor de veiligheid van gene-editing in dieren? Loss of function kan veel trade-offs hebben, kan veel andere effecten hebben. Daarom dit liever niet doen.</p> <p>Bijvoorbeeld editen zodat varkens genetische gecastreerd zijn, om berengeur tegen te gaan: dan zouden de varkens niet in pubertijd komen. Maar ook kunnen ze niet voortplanten, willen we dit? Voortplanten zou dan met ingrepen moeten – daar spelen de nodige ethische dilemma's</p> <p>Ook bij eventuele edits tegen staartbijten spelen ethische dilemma's– technische oplossing voor gedrag dat een symptoom is van problemen in de stal.</p> <p>Oorzaken aanpakken, niet alles oplossen met gene-editing.</p> <p>Liever gain of function, het herstellen van fouten in het DNA.</p> <p>Officieel standpunt is om loss of function niet te gebruiken, tenzij we goed weten hoe alles werkt op DNA niveau en voldoende kennis van biologie en fysiologie hebben om edit volledig te overzien.</p>
A4	<ul style="list-style-type: none"> <li>• Ik zie de veiligheid als de gezondheid en welzijn van het dier. Niet het product. De kans acht hij zeer klein.</li> <li>• Maar niet uitsluiten, dus zorgvuldig testen. Een ingreep in het genoom die niet van nature voorkomt kan gevolgen hebben voor gezondheid en welzijn dier dat vraagt om zorgvuldig onderzoek. Dit is vaak lastig omdat je niet weet waar je naar op zoek moet gaan.</li> </ul>
A5	<p>Wordt niet meegenomen, omdat we ervan uitgaan dat huidige veredeling in runderen gewoon runderen uit voort komen die veilige melk produceren.</p>
A6	<p><i>*Niet specifiek behandeld*</i></p>
Q: When moving from a process-based regulation to a more product-based approach, what should be the basic requirements in terms of safety of new animal products?	
A1	<p>Een basis voorwaarde moet zijn dat een dier aan zijn natuurlijke behoeftes kan voldoen. Als dat gewaarborgd kan worden, is het natuurlijk mooi als de gevoeligheid voor ziektes omlaag gaat.</p> <p>: Bij de AquaAdvantag GMO zalm, is een groeihormoon ingebracht Dat zorgt voor de nodige gedragsveranderingen, zoals dat deze zalm veel minder slaapt</p> <p>Een dergelijke verandering van het dier lijkt me niet wenselijk, omdat het gedrag veranderd is. Het veranderen van de appetite van een kip bijvoorbeeld, lijkt me ook niet wenselijk.</p> <p>Als blijkt dat er, naast het gewenste effect, ook andere negatieve effecten zijn, dan moet je zo'n gene edit niet door willen voeren. Dit zijn wel allemaal aspecten waar je aan de voorkant goed over na moet denken – welke veranderingen mogen wel, en welke niet.</p>
A2	<ul style="list-style-type: none"> <li>• comparative analysis (componenten)</li> <li>• Het goed kunnen functioneren van het dier (dierenwelzijn)</li> </ul>
A3	<p>Gezond boerenverstand, positieve en negatieve kanten afwegen. Voorbeelden staartbijten (liever niet) er (hier wel eens goed naar kijken).</p>
A4	<ul style="list-style-type: none"> <li>• Eerste vraag: wat is het product?</li> <li>• Bij planten is dat het mais in het veld, dus genetisch identieke planten</li> <li>• Bij varkens of koeien in het veld: geen 1 dier is uniek, afgezien van natuurlijke tweelingen</li> <li>• Plantenveredeling: men zet een variëteit op de markt (het product)</li> </ul>

	<ul style="list-style-type: none"> <li>Dat proces kun je niet omzetten naar dieren. Dus wat is het product? Is het een lijn? Er is geen constant product. Melk, vlees, eieren zijn producten, maar hoe bepaald men of het veilig is? Zijn de dieren gezond? Wat is dan precies een product? Dat vraagt interpretatie van dat het is. Elk beest is uniek. Moet je dan elk beest testen? Kijk naar gezondheid van de dieren en wat je verwacht.</li> <li>een regelgeving waarbij je Aquabounty buiten de deur houdt. Proces waarbij dieren gebreken hebben wordt wel uit geselecteerd.</li> <li>Klonen moet je traceren – het is niet te doen maar regelgeving vraagt het</li> <li>Voor dieren naar product-based regeling? Is dat mogelijk als ieder dier een uniek product is – daar kan je niets mee. Code of conduct al van toepassing – manier waarop ze selecties doen. Eisen die je stelt aan oude veredelings technologieën moet je ook voor de nieuwe doen. Verwijst naar afwegingskader Raad voor Dierenaangelegenheden. Wanneer zijn dingen veroorloofd? Dat is niet gericht op 1 techniek.</li> </ul>
A5	Grote aandachtspunt: off target effecten. Heb je niet onbedoeld iets anders geïntroduceerd dan je dacht, dat de veiligheid van het dier in gevaar brengt.
A6	<ul style="list-style-type: none"> <li>Het meest belangrijk is dat het we bij het dier moeten blijven, dus de intrinsieke waarden van het dier en ethisch verantwoord. Men moet hier een afweging maken als het gaat om dierenwelzijn. Genetische castratie (bij varkens, tegen berengeur) en hoornloosheid; zou goed gedaan kunnen worden mbv gene editing. Het zorgt voor een verbetering van het dierenwelzijn bij deze twee voorbeelden.</li> </ul>
<i>Q: Would your concerns be primarily related to the intended effects or to potential unintended effects?</i>	
A1	<p>A1: Mijn zorg is met name voor de onbedoelde effecten. Ik ga ervan uit dat over de bedoelde effecten aan de voorkant al heel goed is nagedacht, voor dat de verandering is doorgevoerd. Je moet daarna dus met name kijken naar onbedoelde effecten.</p> <p>Wij hebben voor ons onderzoek al een screening gedaan van de literatuur, om te zien hoeveel focus er is voor onbedoelde effecten; met name binnen de planten modificatie Daar zien we vooral testen voor de bedoelde effecten</p> <p>A1: Ik ga doordat jullie deze vraag stellen er nu pas goed over nadenken. Een 1e screening is logischerwijs op een beoogd effect, om te zien of je modificatie wel goed is gelukt. Dit zien we ook in onderzoek naar dierenwelzijn, waarbij we bijvoorbeeld de stalinrichting bekijken. Ten eerste kijken we of het welzijn van de dieren daadwerkelijk is verhoogd, ten tweede kijken we naar neveneffecten, zoals emissie, gevolgen voor omwonende etc.</p>
A2	<i>*Niet specifiek behandeld*</i>
A3	<i>*Niet specifiek behandeld*</i>
A4	<ul style="list-style-type: none"> <li>Je begint een traject voor het bedoelde effect.</li> <li>onbedoelde effecten vraagt om zorgvuldig testen</li> <li>Begin niet aan project als je weet dat het een negatieve impact heeft op een ander kenmerk</li> </ul>
A5	zie boven
A6	<i>*Niet specifiek behandeld*</i>
<i>Q: When considering multi-edited GMO events, could you think of situations where segregation of the edits in subsequent generations could lead to safety concerns?</i>	
A1	<i>*Niet specifiek behandeld*</i>
A2	<i>*Niet specifiek behandeld*</i>
A3	<i>*Niet specifiek behandeld*</i>
A4	<i>*Niet specifiek behandeld*</i>
A5	<i>*Niet specifiek behandeld*</i>
A6	<i>*Niet specifiek behandeld*</i>
<i>Op welke manier wordt voedselveiligheid nu meegenomen in de ontwikkeling van nieuwe breeds?</i>	
A4	<ul style="list-style-type: none"> <li>A4 staat ver af van voedselproductie. Zij leveren het genetische materiaal, bijvoorbeeld eieren of kuikens. De relatie met de voedselveiligheid is er niet direct. Dieren die gezond zijn zouden geen bedreiging zijn voor de voedselveiligheid. Zij zorgen ervoor dat de dieren vrij zijn van ziektes die een bedreiging kunnen zijn voor voedselveiligheid (ziektes die zich verticaal kunnen verspreiden in de keten).</li> </ul>
A5	<i>*Niet specifiek behandeld*</i>
A6	<ul style="list-style-type: none"> <li>A6 denkt dat dit al wel gebeurt; noemt als voorbeeld de melkboer die zijn melk verkoopt. Er wordt gezorgd dat de stieren (en de nakomelingen) een goede resistentie hebben voor uierontsteking. Het zorgt voor het verkrijgen van een beter product.</li> </ul>
<i>-Bent u bekend met het concept 'Safe-by-Design'?</i>	
A4	<ul style="list-style-type: none"> <li>Ja, via werkgroep groene biotechnologie met collega's van plantenveredeling</li> <li>Concept spreekt enorm aan</li> <li>Stappen veiligheid gedocumenteerd</li> </ul>
A5	Wel van de term gehoord – maar geen toepassing gezien in de veehouderij.
A6	<ul style="list-style-type: none"> <li>Niet dat A6 weet. Maar als je in de beginfase over de veiligheid voor het dier kan nadenken in de selectie dan is dat mooi meegenomen. Voorbeelden: 1) hoornloosheid is een stuk veiligheid voor het dier en voor de boer en 2) voorkomen berengeur is ook een stuk veiliger en komt kwaliteit van het vlees ten goede.</li> <li>Karakter van het dier is belangrijk – daar kun je ook op selecteren maar men doet het niet.</li> </ul>

### A3.2.4 Economic consequences

*Q: What are your main concerns in terms of economic effects of the increased application of NBTs? Specific examples?*

A1 *\*niet behandeld, buiten de expertise\**

A2 *\*niet behandeld, buiten de expertise\**

A3 Gene drive is zorgelijk, ga ik niet gebruiken. Er zal maar een dier in de natuur terecht komen en kruisen met wilde populaties.

A4 Niet genoemd

A5 In theorie astronomische kansen – core business dieren fokken, en veranderen om ze beter te maken. In theorie is een enorme efficiëntie-slag te maken, dus voor de sector zou dat miljarden kunnen opleveren. Bottleneck blijft: voldoende genen bekend. Winst kan ook bij enkele speler terecht komen, of bij (enkele) spelers buiten Europa.

A6 · A6 maakt zich geen zorgen over de economische effecten; Het bedrijf is een grote speler op de markt (noemt klanten wereldwijd –grote afnemer zijn Brazilië, Rusland o.a.)-. Er zijn zorgen over de manier waarop gene editing gedaan wordt.

*Q: What do you see as the main economic opportunities of the application of NBTs? Specific examples?*

A1 *\*niet behandeld, buiten de expertise\**

A2 *\*niet behandeld, buiten de expertise\**

A3 WE hebben een fokprogramma waar we gebruik maken van genetische variatie, waarmee we de opbrengst kunnen verhogen.

Kunnen we door een gerichte edit dit meer verhogen? Je moet het vaak wel in 3 lijnen aanpassen, edit moet dus wel van waarde zijn om dit rendabel te maken.

Met gene drives zou je wel makkelijker genetische informatie inkruisen, zou heel snel veel geld op kunnen leveren.

Via spermatogonia technieken (monocultures) zou je heel snel 300 individuen met genetische aanpassingen kunnen maken.

A4 · Dit kan forse consequenties hebben. De markt wordt bepaald door de kwaliteit van het product.

· Als concurrent gene edited product heeft, een beter product, dan maakt of breekt het onze marktpositie.

· Afnemers kunnen dus naar het andere betere product omschakelen. Kan enorme impact hebben (dan marktaandeel naar beneden)

A5 *\*Niet specifiek behandeld\**

A6 · Er liggen kansen bij het bedrijf mits we bij de ethische aspecten en intrinsieke waarden blijven. Dus wanneer je bijvoorbeeld minder ingrepen bij het dier hoeft te doen. Maar deze nieuwe technieken moeten op een goede manier gedaan worden; de waarde van het dier moet intact blijven.

*Q: What are your main concerns in terms of economic effects of the current (regulatory) situation with relation to the application of NBTs in plant breeding, in a Dutch and/or European perspective?*

A1 *\*niet behandeld, buiten de expertise\**

A2 *\*niet behandeld, buiten de expertise\**

A3 Wij zitten over de hele wereld, als de concurrent het gebruikt kunnen we heel snel op een achterstand komen.

De selectiepopulatie is naar Canada gebracht, is veiliger (vanwege ziekten o.a.).

Als de EU regelgeving lastig wordt gaan grote bedrijven naar andere werelddelen, zoals VS/Canada, maar daar zitten wij al.

A4 *\*Niet specifiek behandeld\**

A5 Competitieve krachtenveld wordt op de kop gezet. Kapitaalkrachtige organisaties blijven over. Een andere zorg is dat alleen in meest gebruikte rassen worden edits gedaan --> biodiversiteit kan onder druk komen te liggen. Risico op verarming van genetische diversiteit. Deze ontwikkelingen gaan in tegen de maatschappelijke trend van meer lokaal en ambachtelijk.

A6 *\*Niet specifiek behandeld\**

*Q: Where do you see possibilities to benefit from the current (regulatory) situation with relation to the application of NBTs in plant breeding, in a Dutch and/or European perspective?*

A1 *\*niet behandeld, buiten de expertise\**

A2 *\*niet behandeld, buiten de expertise\**

A3 *\*Niet specifiek behandeld\**

A4 *\*Niet specifiek behandeld\**

A5 *\*Niet specifiek behandeld\**

A6 *\*Niet specifiek behandeld\**

*Q: More in general, what are the fields of application of the NBTs that are the most relevant for the Dutch/ European situation? Specific examples? And are there alternative routes to reach the same goals without the use of NBTs? What would be the consequences of the alternative routes?*

A1 *\*niet behandeld, buiten de expertise\**

A2 *\*niet behandeld, buiten de expertise\**

A3 *\*Niet specifiek behandeld\**



A4	*Niet specifiek behandeld*
A5	*Niet specifiek behandeld*
A6	*Niet specifiek behandeld*
Welke (bedrijfseconomische) effecten heeft de (huidige) Europese regelgeving op uw bedrijf? (Bijv. In hoeverre beïnvloedt de Europese regelgeving omtrent GGO's van de EU jullie concurrentiepositie wereldwijd?)	
A4	<ul style="list-style-type: none"> <li>Het huidige klimaat is heel slecht om dit soort dingen te doen</li> <li>Het fundamenteel onderzoek van wat er gebeurt, daar zie je het aan.</li> <li>Leidende onderzoekinstellingen werken hier nauwelijks aan.</li> <li>Bij WUR -microbiologie, [REDACTED]</li> <li>In de dierensector gebeurt er niets</li> <li>Europa: zal achterop lopen op dit terrein wat betreft innovatie. De uitdagingen zijn groot om de wereldbevolking op duurzame manier te voeden.</li> <li>in VS wel</li> </ul>
A5	Op dit moment nog niet. Concurrenten zijn afhankelijk van Amerika. Maar FDA regelgeving ook streng, dus zoveel kan nog niet met dieren in VS. Daar zitten ook vragen over wens van de consument. Geen urgente zorgen, wel op lange termijn. Misschien dat Azië VS en Europa weg zal concurreren, over 10 jaar of meer zou dat plaats kunnen vinden [REDACTED] hoeveel zicht heb je op ontwikkelingen die in Azië plaatsvinden? We hebben niet meer dan jullie, publicaties hebben we en enkele verhalen uit labs. Er is nog niks op de markt
A6	<ul style="list-style-type: none"> <li>Dat kan hij niet helemaal beoordelen. De meeste stieren worden in Amerika gemaakt. De embryo's inplanteren we in VS, op basis van de meeste gezondheidseigenschappen [REDACTED] vraagt of er al gene editing methoden gebruikt worden bij het bedrijf in de VS? Dat kan A6 niet beoordelen</li> </ul>
-Wanneer het bedrijf aan nieuwe technieken werkt – welk deel van het werk aan ggo's/ & genome-editing wordt er buiten de EU uitgevoerd? Wat is daar de oorzaak van?	
A4	<ul style="list-style-type: none"> <li>Het grootste deel buiten. Recombinetics heeft bewezen track record en is in de VS gevestigd. Deels door klimaat Europa. Beter en sneller onderzoek in een ander land. Is er een mogelijkheid, dan doe we het.</li> </ul>
A5	Niet van toepassing
A6	*Niet specifiek behandeld*

### A3.2.5 Regulatory Aspects

Q: When looking at the international perspective, what are your main concerns related to the upcoming application of NBTs in plant breeding? What do you see as the major issues in this respect? Specific examples?	
A1	*niet behandeld, buiten de expertise*
A2	*niet behandeld, buiten de expertise*
A3	Zijn eerder besproken, gene drives zijn zorgwekkend. Vanwege milieueffecten, uitkruisen naar andere rassen
A4	<ul style="list-style-type: none"> <li>al behandeld in andere vragen</li> <li>hoopt dat de opening er komt. Of het dan product-based regelgeving is – is afhankelijk van de definitie van product in de dierensector</li> </ul>
A5	Regelgeving verschilt enorm – snelheden in ontwikkeling. Geen mogelijkheden hier (in EU) om kennis op te bouwen. Australië, Nieuw Zeeland: kleine edits toegestaan (ook in Zuid Amerika), ontwikkelingen in VS Geen level playing field. Geen nieuwe kennis in EU --> op het moment dat het toegepast gaat worden hebben we kennis niet. Genomics nu heel belangrijk: heeft 25 jaar ontwikkeling gehad
A6	*niet behandeld, buiten de expertise*
Q: Do you believe that harmonisation of regulatory requirements is important in this respect? Specific examples to underpin your conviction?	
A1	*niet behandeld, buiten de expertise*
A2	*niet behandeld, buiten de expertise*
A3	Harmonisatie zou heel plezierig zijn, anders wordt je in de verleiding gebracht om technieken juist in andere landen te gebruiken
A4	<ul style="list-style-type: none"> <li>Dat zou fantastisch zijn. Zet er geen cent op in; het gaat niet gebeuren. Daar spelen zoveel belangen, binnen EU is het al lastig genoeg om te harmoniseren. Zaken worden al in handelspolitiek gebruikt. De EU moet zich realiseren, we maar een klein stukje van de wereld zijn.</li> </ul>
A5	Dat zou level playing field genereren – dus heel belangrijk. Kan ook voorkomen dat bedrijven uit Europa weg gaan. Marktleider investeert in gene editing – rekent er op dat gene editing niet zo wordt behandeld als transgenese. In de VS is er een lobby zodat gene editing niet als 'geneesmiddel' behandeld wordt bij dieren.
A6	<ul style="list-style-type: none"> <li>Het afstemmen duurt veel te lang, het zal innovatie belemmeren. Men zal uiteindelijk toch de makkelijkste weg kiezen; als men in VS het op een makkelijker manier kan ontwikkelen, dan zal men daar het bedrijf stichten.</li> </ul>



*Q: What would be your preferred route of harmonising regulatory requirements? Who should take the initiative to come to harmonised requirements? Would you be willing to participate in meetings on harmonisation (should these be organised at some stage)?*

- A1 A1: lastige vraag, ik zou zeggen in eerste instantie op Europees niveau kijken Vanuit Europa uitzoeken wat hier een goede aanpak is. En dan lijkt harmoniseren me een goede aanpak: dat er één loket is waar mensen terecht kunnen
- A2 *\*niet behandeld, buiten de expertise\**
- A3 De EU zou hierin initiatief moeten nemen, afhankelijk van grote handelsbelangen, en kan erg lang duren om dit wereldwijd voor elkaar te krijgen
- A4
- De uitwisseling van data tussen autoriteiten is wenselijk
  - Maar er spelen zoveel belangen bij
  - Het wordt ingewikkelder, bijvoorbeeld door de technieken die buiten EU goedgekeurd zijn en niet binnen EU.
  - De EU gaat reageren met handelsbarrières. Het maakt de wereld er niet beter op.
- A5 Lastige vraag.... Handelsverdragen worden een probleem. Afscherming van de Europese markt staat tegenover wereldhandel. De wereldhandel is een belangrijke reden waarom minister Schouten Europees lobbyt op het gebied van gene editing, om de hele grote Nederlandse plantenveredelingssector te steunen. Ik stel voor: volg landen die je vertrouwt, harmoniseer daarnaar! (bijv. Australië, nieuw zeeland) Gene editing heeft 'vele gradaties', in regelgeving moet wel onderscheid komen, een alomvattende regelgeving gaat niet lukken.
- A6 *\*Niet specifiek behandeld\**
- Consumenten en publieke perceptie, Welke invloed heeft dit op het werk met GGO's? Verschillen nieuwe technieken hierin van oudere technieken?
- A4
- De consument heeft een grote invloed, en terecht. Geldt voor zowel oude als nieuwe technieken
  - Bv vorm van veehouderij, manier van huisvesting, ingrepen al dan niet. Regelgeving op dat vlak heeft oorsprong wat consument vindt · Men moet consument vroeg inschakelen in dialoog. · Veranderingen in dierenproductie – gedreven door grote winkelbedrijven, grote lobbygroepen die bepaalde producten niet meer willen hebben. Het kan veilig zijn, maar als consument het beoordeeld als ongewenst dan gaan ze er niet aan beginnen.
  - Noemt 'Just Editing' project van WUR
- A5 HEEL BELANGRIJK is de publieke perceptie. Wij zijn een coöperatie, dus verschillende percepties zijn voor ons heel belangrijk: van de leden, (burgers, boeren), van de medewerkers, en ook van Friesland Campina. Als melk geproduceerd zou worden door een gene-edited ras en Campina wil dat niet, dan werken wij niet aan de ontwikkeling van dit soort dieren. Wij willen in gesprek (blijven) en de dialoog aan gaan, met de maatschappij. We doen wat de maatschappij wil. Belangrijkste eigenschappen / thema's waarbij gene editen een rol kan spelen? Oplossingen bieden voor methaan emissie, hitte tolerantie, ziekteresistentie Is er ook minder tegenstand vanuit de consument bij aanpassing op deze kenmerken? Heel belangrijk voor vertrouwen van maatschappij (en consument) in degene die de techniek gebruikt – belangrijker dan het vertrouwen in de techniek zelf. Daarom zijn intentie en communicatie heel belangrijk.
- A6
- Wat de consument wil en belangrijk vindt, daar probeer je in het bedrijf naartoe te gaan.
- Voorbeelden: consument wil vlees van Angus koeien en het liefst van koeien die buiten lopen (het Peter's Farm systeem, daar doen ze het al.)

## A3.3 Microbiology Sector Interviews

### A3.3.1 Developments

- General developments
- Q: What do you consider as the most important developments in microbial biotechnology? Specific examples?*
- M1 Focus is nu juist op de non-GM toepassingen, dus de natuurlijke verscheidenheid en adaptatiemethoden. Omzeilt biotechnologie (conventionele GM methoden) en nieuwe methoden (CRISPR-Cas). Dat is wat betreft voeding, dit gebeurt wel voor medische toepassingen. Markt FBR is EU, dus te maken met regelgeving. Biotech wordt in de VS wel toegepast (ook zonder label). EU loopt achter; er is een risico dat er een oneerlijke situatie ontstaat
- M2 CRISPR-Cas technologie. Daarnaast de nieuwe sequentietechnieken zoals Nano-pore, PacBio. Voor micro-organismen is dit makkelijk te doen (bacteriën en schimmels) t.o.v. planten. Met commerciële gewassen heb je vaak te maken met polyploidie; is dus lastiger.
- M3 CRISPR (in het bijzonder cas9) technologie zorgt voor een versnelling van ontwikkelingen in microorganismen. Er waren al veel trucjes om microorganismen aan te passen, CRISPR maakt in sommige organismen nu voor het eerst editing mogelijk – bijvoorbeeld in schimmels waar dit voorheen niet mogelijk was. Ook maakt CRISPR het nu mogelijk om in een paar maanden modificaties te maken die voorheen jaren duurden. Cas12/cpf1 lijkt beter te werken in planten, in tegenstelling tot de veelgebruikte cas9. Dus: Versnelling + goedkoper

M4	<ul style="list-style-type: none"> <li>• snelheid, nauwkeurigheid en multiplexen</li> <li>• snelheid – er komen zaken binnen bereik die 6 jaar geleden experimenteel niet mogelijk waren; bijvoorbeeld meerdere genen in 1 keer aanpassen</li> <li>• multiplexen – als het om kleine selfcloning activiteiten gaat. Die kun je nu heel snel combineren, bijvoorbeeld in bakkersgist. Gemakkelijk op meerdere plekken in het genoom aanpassingen aanbrengen met nauwkeurigheid</li> <li>• je ziet nauwelijks off-targets, niet meer dan met de klassieke methodes</li> <li>• CRISPR/Cas is niet alleen de belangrijkste ontwikkeling, maar ook de mogelijkheid om alles te sequencen</li> <li>• Robotisering is een belangrijke ontwikkeling; zichtbaar bij bedrijven in de VS, hallen met robots voor GM op grote schaal wordt toegepast. Zit in een stroomversnelling.</li> <li>• De technologie verandert, dit resulteert in verhoogde snelheid en complexiteit van ingrepen, maar geen fundamentele waterscheiding. In 40 jaar geen enkel incident geweest waarbij microbiële biotechnologie leidde tot incidenten met veiligheid. Na 40 jaar kun je zeggen dat de risico's niet zijn toegenomen.</li> <li>• Men moet verstandig met deze technologieën omgaan – maar dat geldt voor elke technologie.</li> </ul>
M5	<p>de synthetische biologie toolbox</p> <ul style="list-style-type: none"> <li>• deze toolbox is de afgelopen 10 jaar bij elkaar gekomen</li> <li>• het is een combinatie van bouwen, inbrengen &amp; controle</li> <li>• het geeft de mogelijkheid om micro-organismen te veranderen door gebruik te maken van gesynthetiseerde DNA constructen</li> <li>• vervolgens is een controle door sequencing; het exact bepalen wat er aangepast is in het genoom, conform wat bedoeld is</li> </ul>
M6	Ontwikkeling van genetische gereedschappen zoals CRISPR-Cas, recombinering. Ontwikkelingen op het gebied van automatisering/robotics voor stamontwikkeling. Ontwikkeling van microorganismen die bijdragen aan de circulaire economie en de VN Duurzame Ontwikkelingsdoelstellingen (SDG).
M7	CRISPR-Cas, veel voorbeelden van in non-industrial labs. Maar we passen het zelf niet toe, vanwege de onduidelijke patenten positie en de ontwikkelingen in EU qua regelgeving. Het is een te groot risico als start-up bedrijf om het te gebruiken. • Het bedrijf is nog te klein om CRISPR op grote schaal te implementeren en het kan jaren duren om het goed in de vingers te krijgen. Risico van implementatie van technologie in pril stadium in een start-up bedrijf. • De CRISPR-technologie heeft enorme potentie, er zijn nu allemaal varianten van Cas enzym. De technologie ontwikkelt zich nog steeds; het wordt steeds preciezer. Grote bedrijven zijn daar zeker mee bezig en houden rekening met patenten etc. • Uitspraak EU hof positioneert EU ongunstig ten opzichte van andere grote landen; VS/China.
<i>Q: What do you see as the most beneficial developments? Specific examples?</i>	
M1	Meest gunstig: van allerlei microbiomen snel het genoom bepalen; en daarna vaststellen wat de meest interessante organismen zijn (non-GM). Kan nog niet gebruik maken van CRISPR-Cas. teleurstellend: constateren 'gevaaren' GMO technologieën, gebeurde 40 jaar geleden ook al. Nu nog last van terwijl techniek beter is geworden.
M2	CRISPR-Cas technologie: is natuurlijk fantastisch maar het werkt nog niet, alleen nog voor een paar paddenstoelvormige schimmels. De mogelijke onbedoelde effecten zijn nog onbekend. Nog niet echt in opmars in Europa door strenge regelgeving (strenge regelgeving is niet logisch). Deze technologie werkt nog niet in veel paddenstoelen en mag je in de EU niet zomaar toepassen voor voedselproducten.
M3	Strikte GMO regelgeving voor grote veranderingen, bijvoorbeeld invoegen van een transgen zoals Bt toxine, is prima
M4	<i>*zie antwoord hierboven*</i>
M5	<i>*zie antwoord hierboven*</i>
M6	De ontwikkelingen op het gebied van sequencing die de kosten drastisch verlaagd hebben en de toegankelijkheid tot de technologie verhoogd. Illumina sequencing, PacBio sequencing en Nanopore sequencing.
M7	<ul style="list-style-type: none"> <li>• Next gen sequencing, kan sneller en goedkoper dan voorheen met goede accuracy en annotaties. Prijzen gaan jaarlijks naar beneden, bedrijven kunnen specifieke services leveren voor start-ups die dat nodig hebben.; • LC-MS proteomics, voor verzamelen data novel foods dossier.</li> </ul>
<i>Q: What do you see as developments of concern? Specific examples?</i>	
M1	Noemt biotech ontwikkelingen in China (misschien zal EU achter blijven) en dat wij daar niet op de hoogte van zijn, maar gelooft niet dat producten gevaren kunnen ontstaan voor mens en dier ( <i>En teleurstelling negatieve imago GMO technologie van vorige vraag</i> )
M2	Door de strenge regels vertraagt het innoveren, men moet meer kijken naar het product zoals dat in andere landen gebeurt. Voor veel bedrijven is dit zorgelijk en komt de concurrentie positie in het geding.
M3	Kleine edits en introduceren van genen binnen eigen soort (cisgenese) maar ook inactiveren van genen door indels/frameshifts zou niet onder strikte GMO regelgeving moeten vallen. Regelgeving in EU is zo veel strenger dan in andere landen terwijl CRISPR technologie kan meehelpen om de voedselvoorziening in de wereld te verbeteren. Planten kunnen hierdoor bijvoorbeeld worden aangepast dat ze kunnen groeien in het veranderende klimaat (denk aan hitte, veranderende bodemcondities; droogte/zoute grond etc.) en bescherming tegen pathogenen.

M4	<ul style="list-style-type: none"> <li>• het valt mee met de zorgelijke ontwikkelingen. Microbiële biotechnologie, met inbegrip van GMO, is niet meer uit ons leven weg te denken – met uitzondering van levensmiddelenbiotechnologie.</li> <li>• Zorgelijke ontwikkeling no 1.: het magisch wereld beeld rond voeding ('biologisch', 'natuurlijk', dat, eeuwen na de Renaissance, nog steeds een 'levenskracht' aan moleculen toe blijft kennen ('natuurlijke suikers', etc.), lijkt eerder sterker dan zwakker te worden.</li> <li>• in de discussie over veiligheid van genetische modificatie van levensmiddelen gaat het allang niet meer om rationele risicoanalyse. Het gaat meer om de emotie. Emotie heeft een plaats in het maatschappelijk debat, maar als je dit gaat mengen met inhoudelijke argumenten, dan krijg je hele rare discussies.</li> <li>• Bioterrorisme is een potentiële bron van zorg, maar daar heb je echt geen GGO's voor nodig (noemt enkele niet-GGO scenario's).</li> <li>• GM technologie wordt 4 decennia lang op gigantische schaal toegepast; er is niets gebeurd (geen incidenten).</li> <li>• door voorzichtig te zijn, en door ons teveel te laten leiden door emoties en niet-wetenschappelijke beslissingsprocessen, kun je de maatschappij mogelijkheden ontzeggen om echte stappen te maken op gebieden als duurzaamheid, ontwikkeling van vleesvervangers, etc.</li> <li>• in Europa hebben we de wetten ingedeeld op processen niet het resultaat; uiteindelijk is het niet meer rationeel wat we aan het doen zijn</li> </ul>
M5	<ul style="list-style-type: none"> <li>• ethische aspecten – wat wil je precies?</li> <li>• bijvoorbeeld, gebruik CRISPR-Cas technologie in de mens is zorgwekkend</li> <li>• en het gebruik van gene drives, dus de mogelijkheden om epidemieën te bestrijden</li> <li>• nieuwe technologische mogelijkheden brengen nieuwe ethische en veiligheidsdiscussies</li> <li>• het kan te ver doorschieten; daar moeten we als wereld goed over nadenken</li> </ul>
M6	De onwerkbaar proces-gebaseerde GMO regelgeving in Europa in vergelijking met die in de rest van de wereld. De uitspraak van de EUCJ heeft dit verder op scherp gezet. Op papier van alles mogelijk, in praktijk moet je aan extra zaken voldoen, onrendabel om dingen in gang te zetten. GMO label maakt product lastig op de markt te brengen
M7	<ul style="list-style-type: none"> <li>• Public opinion tegen GMOs, vooral binnen Europa. Het ligt gevoelig bij consument. • Als het product is goedgekeurd dan zou het publiek zich niet zo snel zorgen moeten maken, veel producten bevatten al enzymen van GMOs (voorbeelden die worden genoemd: rennet voor kaas en pectinases in sappen).</li> <li>• Interessant om wetgeving te volgen, bijvoorbeeld labeling 'made with/from GMO' en organic foods etikettering.</li> <li>• De vraag die we onszelf moeten stellen: kan er zonder GMO tools wel dezelfde sustainability doelen gehaald worden?</li> </ul> <p><i>Q: What do you see as a realistic timeline for: o gene edited micro-organism-containing or derived products moving to the European market based on base editing?</i></p>
M1	Die zijn er vast al, bijvoorbeeld gefermenteerde producten (noemt Azië hier. Niet uit VS maar zou kunnen. Ketjap, Kim-chi. Producten die op grote productieschaal worden verkregen)- voor non-food/medicijnen geen probleem. Als het betaalbaar is dan GMO, dan geen probleem - producten die te maken hebben met duurzaamheid (maken chemicaliën, GMO geen probleem voor publiek)
M2	in de medische sector: veel toegestaan (heeft het nogmaals over de publieke acceptatie). Uiteindelijk zal het wel voor de voedselproductie gebruikt worden. Het zal afhankelijk worden van de noodzaak; het wordt dus markt-afhankelijk. Noemt als voorbeeld de landen die afhankelijk zijn van bepaalde voedselbronnen (bijv. rijst) en als er schaarste is zal men GGO eerder accepteren. - Hangt sterk af van het product en de noodzaak om dit te ontwikkelen (champignon productie/markt is al verzadigd bijvoorbeeld, de noodzaak is hier dan ook klein)
M3	Producten gaan waarschijnlijk wel uiteindelijk op de markt komen, dit gebeurt nu nog heel weinig maar op het gebied van CRISPR technologie in microorganismen gebeurt nu wel gigantisch veel. Voor productieorganismen zal het geen issue worden (ook niet voor het publiek). Waarschijnlijk eerste producten over 5-10 jaar, grote bedrijven zullen geen last hebben van de regelgeving omdat zij de kosten voor dossiers wel kunnen dragen (bijv. de Monsanto's), de regelgeving is juist 'killing' voor de kleinere verdelers.
M4	die zijn al op de markt. Noemt geneesmiddelen, cosmetica <ul style="list-style-type: none"> <li>• Europese markt? Veelal enzymen die met GMO's gemaakt zijn en waarschijnlijk ook met CRISPR-Cas</li> <li>• er zijn nu grote projecten rondom sweeteners die mbv GMO's gemaakt worden.</li> <li>• als het gaat om flavors en fragrances; kan niet voorstellen dat het zonder GM gaat.</li> <li>• GM wijngisten zijn op de markt. Biergisten ook – maar niet in Europa.</li> <li>• In Europa: toepassing in de levensmiddelenindustrie wordt geblokkeerd. Moet zich voor de consument vooral profileren als ambachtelijk en natuurlijk (noemt bier- en zuivelindustrie als voorbeelden).</li> </ul>
M5	<ul style="list-style-type: none"> <li>• afgeleide producten van GGO's zijn allang op de markt (bijvoorbeeld chymosine)</li> <li>• ook gene edited micro-organismen zijn op de markt</li> <li>• syn bio producten zijn, naar zijn weten, niet op de markt</li> </ul>
M6	De EU maakt geen onderscheid tussen CRISPR-Cas en traditionele GMO technieken. Voor introductie in het milieu: met de huidige wetgeving is dit mogelijk, maar zijn de goedkeuringsprocedure (met milieu risico analyse en meldingsplicht bij het lidstaat van de eerste introductie waarna EFSA er goedkeuring over moet geven, en het



	opstellen van een monitoringsplan) en verplichte gmo labeling zijn redenen dat weinig bedrijven hiertoe over zullen gaan; bij wijziging van de wetgeving waarbij deze technologie een uitzonderingspositie zou krijgen net als klassiek mutagenese is dat wellicht na 5-10 jaar. Voor contained use waarbij het product geen biomassa bevat zou het al toegepast kunnen worden. Ook afgedood materiaal van gmo productiestammen kan gebruikt worden.
5.1.2	• In de rest van de wereld: in de VS wordt naar product gekeken, • Er wordt met twee maten gemeten, traditionele mutagenese versus nieuwe targeted methoden
M7	<i>*niet specifiek behandeld*</i>
	<i>o gene edited micro-organism-containing or derived products moving to the European market based on HDR procedures?</i>
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet behandeld, zie hierboven*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet behandeld, zie antwoord hierboven*</i>
M5	<i>*niet behandeld, zie antwoord hierboven*</i>
M6	De EU maakt geen onderscheid tussen CRISPR-Cas en traditionele GMO technieken. Voor introductie in het milieu: met de huidige wetgeving is dit mogelijk, maar zijn de goedkeuringsprocedure (met milieu risico analyse en meldingsplicht bij het lidstaat van de eerste introductie waarna EFSA er goedkeuring over moet geven, en het opstellen van een monitoringsplan) en verplichte gmo labeling zijn redenen dat weinig bedrijven hiertoe over zullen gaan. Voor contained use waarbij het product geen biomassa bevat zou het al toegepast kunnen worden. Ook afgedood materiaal van gmo productiestammen kan gebruikt worden.
M7	• EU is hierin niet de voorloper, CRISPR-Cas producten voorlopig niet. Plantenbedrijven hebben wel de grootste behoefte voor het kunnen toepassen van gene-editen. Voor de dieren- en microbiële sector weet ik dit niet. VS loopt al voor op EU; de toepassing van deze technologie vindt al plaats (veel start-ups). • Goedgekeurde producten in VS, moeten voor export wel eerst in EU worden gekeurd. Ook wanneer producten in VS als non-GMO worden gezien, deze producten moeten aan EU regels voldoen; exporteurs lopen risico als dit ongeautoriseerd wordt verhandeld. Wellicht ook in China, maar lastig informatie over te krijgen. • casus: soja wat gene-edited is, maar niet aan te tonen, dus het kan mogelijk in exportstromen terecht komen.
	<i>o synthetic biology products, with characteristics unknown to nature, moving to the European market?</i>
M1	in de medische sector: veel toegestaan (heeft het nogmaals over de publieke acceptatie). Uiteindelijk zal het wel voor de voedselproductie gebruikt worden. Het zal afhankelijk worden van de noodzaak; het wordt dus markt-afhankelijk. Noemt als voorbeeld de landen die afhankelijk zijn van bepaalde voedselbronnen (bijv. rijst) en als er schaarste is zal men GGO eerder accepteren. Hangt sterk af van het product en de noodzaak om dit te ontwikkelen (champignon productie/markt is al verzadigd bijvoorbeeld, de noodzaak is hier dan ook klein
M2	? Zelfde antwoorden als M1; wat is hier misgegaan?
M3	<i>*niet behandeld, zie hierboven*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*zie antwoord hierboven*</i>
M6	Dit zie ik niet zo snel gebeuren. Minimaal 15 jaar. Een recent EFSA supporting document van Cécile van der Vlugt onderstreept dat er binnen 10 jaar nog weinig te verwachten is.
M7	<i>*niet specifiek behandeld*</i>
	<i>Q: What do you see as major issues when comparing the current basically process-based regulations versus an alternative product-based regulations?</i>
M1	Wellicht kijkt een product-gebaseerde methode meer naar de relevante eigenschappen dus komt ten goede van de veiligheid
M2	M2 noemt wel dat men in Europa zal gaan achterlopen door de publieke acceptatie (mensen zullen niet gauw overstappen naar een gene-edited variant van een product omdat er geen noodzaak is).
M3	<i>*niet specifiek behandeld*</i>
M4	<ul style="list-style-type: none"> <li>• voorkeur: de product-gebaseerde regelgeving</li> <li>• dat voorkomt rare situaties. Noemt product voorbeeld: yoghurt met GM probiotica. In de EU wordt dit niet verkocht omdat het, volgens EU regelgeving, een GGO product is, maar Europeanen kunnen het in de USA wel eten, waardoor de levende bacteriën in hun darm mee terug nemen.</li> <li>• noemt belang internationale handel</li> <li>• verschillen leiden tot onproductieve spagaten: het is mogelijk om twee micro-organismen te maken waarvan alle miljoenen letters van het DNA identiek zijn – terwijl de 1 een GGO is en de andere niet.</li> <li>• nieuwe technologieën bieden mogelijkheden om voor de consument en maatschappij belangrijke veranderingen aan te brengen.</li> <li>• als je wilt zoeken naar risico's dan kun je ze voor elke technologie vinden. 0 risico alleen bij 0 Kelvin – en dan beweegt er niets meer</li> <li>• Noemt voorbeeld klassieke mutagenese en het risico dat je per ongeluk een gencluster voor toxine productie kan aanzetten – heeft in 70 jaar van toepassing niet tot problemen geleid.</li> </ul>

	<ul style="list-style-type: none"> <li>• dus kijk naar het product en niet proces waarmee het gemaakt is</li> <li>• Het is anders bij modificaties in dieren, waar dierenwelzijn in het geding kan zijn.</li> </ul>
M5	<ul style="list-style-type: none"> <li>• bij een product gebaseerde regelgeving: minder problemen</li> <li>• het laat toe om een veilige techniek te gebruiken i.p.v. een 'uit de regelgeving gewenste' techniek</li> <li>• technologisch kunnen we veilige sequenties gebruiken en in het genoom inbouwen</li> <li>• met traditionele mutagenese heb je die controle minder</li> <li>• je moet heldere regelgeving hebben</li> <li>• je kunt de afweging 'hoe maak ik mijn product zo veilig mogelijk' maken met de nieuwe technieken</li> <li>• het minst rationele zijn de klassieke methoden, vanwege de vele random mutaties</li> <li>• internationale harmonisatie is van belang; alleen specifieke producten voor bepaalde landen ontwikkelen, vanwege de regelgeving, is niet gewenst. Kapitaalintensief traject: kan niet voor een klein deel van de wereld</li> </ul>
M6	<i>*niet specifiek behandeld*</i>
M7	<i>*niet specifiek behandeld*</i>

### A3.3.2 Traceability

	<i>Q: Do you see possibilities for the development of detection methods (PCR-based?) for gene edited micro-organisms?</i>
M1	Bij product-based wellicht niet meer nodig? Richten op toxiciteit bij handhaving van belang. Traditionele stamverbeteringsmethoden leiden ook tot veel grote genetische veranderingen word nu niet op gecontroleerd.
M2	Als een bedrijf zijn breedingshistorie publiceert, dan wel. Dus documentatie = traceerbaarheid. M2 zegt de mogelijkheid er is om GMO wetgeving te omzeilen door CRISPR-Cas mutant te doen laten lijken op traditional breeding variant (fraude is dus onmogelijk aan te tonen). Niet specifiek methoden, maar juist documentatie van ontwikkeling van de GMO door producent (traceability)
M3	WGS/sequenzen, hiermee zijn alle kleine edits wel op te sporen maar het onderscheid maken met natuurlijke variatie is lastig / niet mogelijk.
M4	<ul style="list-style-type: none"> <li>• Ja, dmv van bewust de genetische modificaties uitvoeriger maken</li> <li>• Watermarking</li> </ul> <p>o dit is een markering, een codonverandering, zonder dat je het gecodeerde eiwit verandert. Dus bewust informatie toevoegen. Je modificeert meer dan nodig met als enige doel om barcode toe te voegen – zonder dat dit beïnvloedt hoe het DNA wordt afgelezen</p> <p>o dus extra informatie invoegen om het traceerbaar te maken; dat is heel goed mogelijk</p>
M5	<ul style="list-style-type: none"> <li>• dat kan</li> <li>• genome editing laat hele precieze modificaties toe; motivatie om self-clonings producten te maken</li> <li>• je kunt prima een barcode toevoegen, dus een stukje synthetische sequentie aanbrengen</li> <li>• vanuit technologisch en regulatorisch oogpunt is dat ongewenst; voeg niet iets toe wat geen functie heeft, dus zo min mogelijk aanpassingen</li> <li>• maar je kunt een barcode maken van de aanwezige sequentie, die je op een snelle manier gerecombineerd waardoor je geen soortvreemd DNA inbrengt.</li> </ul>
M6	Als je weet welke edit dit is kan het met sequencing aangetoond worden. Je kan alleen nooit hard maken dat dit geen spontane mutanten zouden kunnen zijn.
M7	Volgens mij wel, bijvoorbeeld door korte sequenties/barcodes achter te laten. • Het is wellicht mogelijk om bijvoorbeeld bedrijf-specifieke codes gebruiken in bepaalde producten. Maar dit zal niet mogelijk zijn voor gezuiverde producten (zonder levende mo of DNA). • Zien geen veiligheidsissues om kleine barcodes te gebruiken.
	<i>Q: - Do you see options for traceability of multi-edited micro-organisms?</i>
M1	<i>*niet behandeld, zie vraag hierboven*</i>
M2	<i>*niet behandeld, zie vraag hierboven*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	<i>Expert gaf hetzelfde antwoord als hierboven: als je weet welke edits dat zijn kan het met sequencing aangetoond worden Je kan alleen nooit hard maken dat dit geen spontane mutanten zouden kunnen zijn</i>
M7	<i>*niet specifiek behandeld*</i>
	<i>Q: - Do you see possibilities for the traceability of specific traits? If so, what do you see as bottlenecks for adequate tracing of traits of potential concern?</i>
M1	<i>*niet behandeld, zie vraag hierboven*</i>
M2	<i>*niet behandeld, zie vraag hierboven*</i>
M3	<i>*niet behandeld*</i>
M4	<ul style="list-style-type: none"> <li>• proteomics en metabolomics in kaart brengen.</li> <li>• snelle profilering van wat er in een organisme veranderd is</li> </ul>

	<ul style="list-style-type: none"> <li>• puur integriteit van bedrijven omgang met wetten en regels; Westerse bedrijven nemen dat risico niet. Ze weten precies wat de risico's zijn, zowel juridisch als beeldvorming bij consumenten.</li> </ul>
M5	<ul style="list-style-type: none"> <li>• M.b.v. precieze genoom engineering: 'self-cloning-achtige' organismen maken waar je geen soortvreemd DNA inbrengt</li> <li>• dit is niet te onderscheiden: vanuit eigenschap is dat heel lastig aan te geven welke methode je hebt gebruikt</li> <li>• vanuit risico-oogpunt zou je het beste naar resultaat moeten kijken</li> <li>• aantal criteria waar je aan moet voldoen, voorbeeld van herbicide resistentie bij planten wordt genoemd. Dus wat zijn de risico's? Belangrijk: 1) kijken naar de aanwezigheid van ingebrachte sequenties in een plant en 2) de mogelijkheid van verspreiding van de eigenschap</li> </ul>
M6	Dit ligt zeer aan de eigenschap. Antibiotica resistenties en antimicrobial productie kunnen getest worden als je te maken hebt met levende biomassa. Specifieke genen zijn middels sequencing of PCR te detecteren als ze boven een detectielimiet aanwezig zijn.
M7	<i>*niet specifiek behandeld*</i>
	<i>Q: In your view, what should be the consequence of a possible product-based approach in terms of traceability, in other words, what would still be relevant for monitoring programmes?</i>
M1	<i>*niet behandeld, zie vraag hierboven*</i>
M2	<i>*niet behandeld, zie vraag hierboven*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	<i>*niet specifiek behandeld*</i>
M7	<i>*niet specifiek behandeld*</i>

### A3.3.3 Safety

	<i>Q: What do you see as the major issue(s) when considering the safety of gene edited micro-organisms?</i>
M1	- Controleren op toxische bijproducten bij mo's voor voedingsproducten. Niet bang voor overdracht DNA op andere organismen.; Dit is toepassingsafhankelijk. In het algemeen: belangrijk om te screenen op toxische bijproducten
M2	Naar het product zelf kijken; dus de genoomsequentie bekijken en de veranderen die zijn aangebracht (bedoeld en onbedoelde effecten). En het organisme bestuderen in de context waarin je het wilt gebruiken (noemt dat genetische gemodificeerde gewassen bijvoorbeeld een ecologische consequenties kan hebben, maar dit moet wel bestudeerd worden zoals het in de natuurlijke situatie is). Kijk juist naar het product, genoom sequentie van mutant. Onderzoeken van veiligheid van het organisme, bijvoorbeeld groei van een plant in het veld en effect op natuurlijke populaties.
M3	Off-targets zijn te controleren en vaak geen issue door te selecteren na sequenzen en het uitkruisen van deze ongewenste mutaties. Microorganismen die grote edits hebben moeten goed getest worden op veiligheid, daarnaast kan gezorgd worden dat deze organismen niet meer in het eindproduct aanwezig zijn. Op deze manier ervoor zorgen dat er geen ondoordachte dingen gedaan worden om het publiek gerust te stellen.
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	Veiligheid van genome-editing verschilt niet van die van traditionele mutagenese technieken en die hebben een historie van veilig gebruik. moet qua veiligheid op dezelfde manier worden behandeld
M7	<ul style="list-style-type: none"> <li>• Bijvoorbeeld voor ovalbumine, o Eerst onderscheid maken; 'from GMO' en 'with GMO'. With gmo betekent dat er geen GMO meer aanwezig is in het product; in geval van from gmo is er specifieke wetgeving 1829/2003. o Ook EFSA guidance gebruikt om te kijken of eindproduct een enzym/additive/novel food etc. is. o Waar zijn wij met ons product Het is geproduceerd 'with GMO', bevat geen materiaal meer uit micro-organisme; is wel novel food, geproduceerd met nieuwe procedure o Volgen novel food regelgeving, deel hierin beschrijft productie met GMOs,</li> <li>• Ons voorbeeld laat zien dat het is complex proces is voor bedrijven. Het vereist het doornemen van regelgevingen &amp; guidances/opinies van EFSA. Het is verwarrend voor de gebruikers omdat niet alles duidelijk beschreven staat, met name in de novel food richtlijnen. • Een duidelijk overzicht zou dit proces makkelijker maken, bijvoorbeeld een beslisboom. Of men moet nadenken over het ontwikkelen van een platform/klankbord voor bedrijven voor informatieuitwisseling.</li> </ul>
	<i>Q: - When moving from a process-based regulation to a more product-based approach, what should be the basic requirements in terms of safety of new products?</i>
M1	protocol aanleveren: definiëren producten, dus de componenten. Relevante cellijnen voor het testen van humane toepassingen



M2	Welke genen er zijn veranderd. De bedoelde en onbedoelde effecten (off-target effecten kunnen in een gen zitten). Noemt een voorbeeld van een onbedoeld effect in een gen dat codeert voor een glucosidase – met als gevolg een verandering in de celwandcompositie van een schimmel. Hiermee heb je niet aan de standaard compositieanalyse (wordt niet specifiek naar gekeken). Voor paddenstoelen zouden er andere eisen gesteld kunnen worden, maar er is nog weinig bekend in dit veld; van de meeste genen weten ze nog niet wat ze doen. -Aantonen welke genen veranderd zijn, zowel de bedoelde als onbedoelde mutaties. -De beoogde productiemethoden. Bijvoorbeeld, zware metalen kunnen accumuleren. Het is goed om dit te monitoren mbv content analyse.
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<ul style="list-style-type: none"> <li>• modificatie die je aanbrengt moet minimaal zijn en precies zijn wat de intentie is</li> <li>• geen antibioticamarkers aanwezig</li> <li>• risico's minimaliseren – maar is organisme specifiek. Bijvoorbeeld, QPS organismen behandel je anders dan niet QPS organismen, case-by-case evaluatie</li> <li>• de huidige praktijk van kruisen en breeding is minder rationeel dan genome editing</li> <li>• grootste heikelpunt is de consumenten perceptie ('frankenfood' beeld bij de consumenten)</li> <li>• in de foodhoek hebben wij er heel veel mee te maken</li> <li>• vooral emotionele discussie, niet rationeel</li> <li>• publiek wil vooral ambachtelijke producten</li> <li>• technologisch kunnen het met de autoriteiten eens worden, maar publiek is een grote stakeholder in deze discussie</li> <li>• in VS heb je dezelfde typische spagaat; er zijn twee kampen (polarisatie)</li> </ul>
M6	De veiligheidseisen van het product zouden niet afhankelijk moeten zijn van de technologie waar het mee verkregen is en dus product specifiek moeten zijn. <ul style="list-style-type: none"> <li>• Wat zijn de eisen voor het product, waar moet het aan voldoen</li> <li>• Wat is de mogelijke impact van de verandering op de gestelde veiligheidseisen</li> <li>• In het extreme zou je alle nieuwe producten moeten testen, waarschijnlijk niet werkbaar</li> <li>• Logischerwijs bekijken wat de belangrijkste potentiële risico's zijn</li> </ul>
M7	• Data over de veiligheid van het micro-organisme; virulentie, infectiviteit, allergeniciteit etc. • De aanwezigheid organisme in het eindproduct; zijn er levende micro-organismen aanwezig of niet?
<i>Q: Would your concerns be primarily related to the intended effects or to potential unintended effects?</i>	
M1	meer zorgen over de onverwachte effecten. Fermentaties (substraten) waar niet eerder op gegroeid is geen historie, komen elkaar in de natuur niet tegen (dus meer in de richting van de Novel Foods)
M2	<i>*Zie antwoord hierboven*</i>
M3	Unintended effects kan je goed controleren, er zijn bijvoorbeeld ontwikkelingen (vooral bij cas9) die de nauwkeurigheid van de techniek vergroten. Bijvoorbeeld door protein engineering van cas9 en de ontwikkeling van natuurlijke cas9 varianten die nauwkeuriger zijn.
M4	<ul style="list-style-type: none"> <li>• in de voedingssector; niet zo bang dat onbedoelde effecten negatieve gevolgen zullen hebben</li> <li>• het is zo dat elke verandering een risico met zich mee brengt, maar maakt zich geen zorgen</li> <li>• onbedoelde effecten zijn net iets risicovoller</li> </ul>
M5	<ul style="list-style-type: none"> <li>• onderdeel van de toolbox is de stammen volledig controleren</li> <li>• als ze iets onverwachts zien: stam wordt weggegooid</li> <li>• off-target effecten zijn een risico, maar daar wordt op gecontroleerd</li> </ul>
M6	Persoonlijk heb ik geen zorgen wat betreft veiligheid. Bedoelde effecten zouden veilig ontworpen moeten zijn. Ik heb geen voorbeelden van onbedoelde effecten met betrekking tot voedselveiligheid die tot nu toe aan het licht gekomen zijn. Ook hier is er een historie van veilig gebruik. <ul style="list-style-type: none"> <li>5.12 e • In microorganismen wordt alles gesequenced, alle effecten in kaart gebracht, • Geen zorgen over de veiligheid, zeer goed beheersbaar</li> </ul>
M7	• Grootste zorg zijn de onbedoelde effecten, bedoelde effecten zijn beter onder controle te houden. • Onbedoelde effecten zouden kunnen zijn: o het activeren van de productie van mycotoxines o het ontsnappen van een GM micro-organisme uit contained use, wat een milieurisico zou kunnen zijn
<i>Extra vraag bedrijven: op welke manier wordt voedselveiligheid nu meegenomen in de ontwikkeling van nieuwe genetisch gemodificeerde micro-organismen (GMMs)?</i>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<ul style="list-style-type: none"> <li>• technologie gebruiken voor nieuwe organismen – je kunt bijvoorbeeld genclusters voor toxine productie uitschakelen</li> <li>• mbv de moderne technologieën: off-target effecten die een orde van grootte lager is vergeleken met de traditionele mutagenese technieken. Met WGS kun je kijken wat er is gebeurd op DNA niveau. Dus gericht dingen</li> </ul>

	eruit screenen met moderne technieken (mbv hulp robotica). Veiligheidsrisico's worden, mede door deze extra controle, nog kleiner.'
M5	<ul style="list-style-type: none"> <li>• ziet weinig risico's</li> <li>• doden alle micro-organismen af</li> <li>• marker-vrije stammen - bevatten geen antibiotica resistentie genen</li> <li>• het risico van toxine productie kan uit stammen gehaald worden – dus de rationele risico's kan men uit de stammen halen</li> <li>• alle risico's kun je tackelen met de nieuwe technologieën</li> <li>• het risicoprofiel daalt</li> </ul>
M6	De regelgeving van gmms is zeer duidelijk. Mocht een gmm ontwikkeld worden voor levensmiddeltoepassingen dan wordt hier vanaf het begin rekening mee gehouden.
	<ul style="list-style-type: none"> <li>• Enzymen: productie in contained use, wordt gezuiverd: processing aid</li> </ul>
M7	· Er wordt bij het product op meerdere vlakken naar veiligheid gekeken, bijvoorbeeld naar allergeniciteit, peptide-scanning. Er worden ook geen antibiotica markers gebruikt.

### A3.3.4 Economic consequences

<i>Q: What are your main concerns in terms of economic effects of the increased application of NBTs? Specific examples?</i>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	Een zorg is dat de huidige ggo wetgeving de komende jaren nog van kracht blijft en op deze manier de innovatieve slagkracht van de Europese sector benadeelt.
M7	<i>*niet specifiek behandeld*</i>
<i>Q: What do you see as the main economic opportunities of the application of NBTs? Specific examples?</i>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	Als we een product gedreven gmo wetgeving zouden krijgen zal genome editing sneller tot een gewenst resultaat kunnen leiden dan klassieke mutagenese. Bijkomend voordeel is dat alleen de beoogde mutaties worden doorgevoerd en je geen last hebt van mutaties die een negatief effect hebben op de overall fitness van het productieorganisme. Sneller en beter dus.
M7	<i>*niet specifiek behandeld*</i>
<i>Q: - What are your main concerns in terms of economic effects of the current (regulatory) situation with relation to the application of NBTs in plant breeding, in a Dutch and/or European perspective?</i>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	<i>*niet specifiek behandeld*</i>
M7	<i>*niet specifiek behandeld*</i>
<i>Q: Where do you see possibilities to benefit from the current (regulatory) situation with relation to the application of NBTs in microbiology, in a Dutch and/or European perspective?</i>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	<i>*niet specifiek behandeld*</i>
M7	<i>*niet specifiek behandeld*</i>



<p><i>Q: More in general, what are the fields of application of the NBTs that are the most relevant for the Dutch/ European situation? Specific examples? And are there alternative routes to reach the same goals without the use of NBTs? What would be the consequences of the alternative routes?</i></p>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	<i>*niet specifiek behandeld*</i>
M7	<i>*niet specifiek behandeld*</i>
<p><i>Extra vraag bedrijven: Bent u bekend met het concept 'Safe-by-Design'? (Zo ja, wat is het? Evt antwoord aanvullen. Zo nee, kunt u een toelichting geven?) In hoeverre wordt dit al toegepast in de praktijk?</i></p>	
M1	<i>*niet behandeld*</i>
M2	<i>*niet behandeld*</i>
M3	<i>*niet behandeld*</i>
M4	<i>*niet behandeld*</i>
M5	<ul style="list-style-type: none"> <li>• gestandaardiseerde elementen gebruiken in een bekend proces</li> <li>• dan kun je er van uitgaan dat nieuwe combinaties veilig zijn in lab en in de fabriek.</li> <li>• in systematiek bedrijf ingebouwd: vanuit productieschaal terugwerken.</li> <li>• alles wat we in het lab doen, houden we rekening mee dat het op de markt komt (bijvoorbeeld rekening houden met de veiligheid)</li> <li>• is intrinsiek onderdeel van manier van werken in bedrijven</li> <li>• downscalen - beginnen aan de achterkant en hoe we op het lab moeten beginnen</li> <li>• Dus veiligheid is een belangrijk onderdeel en er wordt rekening mee gehouden.</li> </ul>
M6	Safe-by-design betreft het inbouwen van specifieke eigenschappen die er voor zorgen dat het micro-organisme alleen onder specifieke kweekcondities die in de fermentor aangelegd worden kan overleven, maar niet daarbuiten. Ik ken geen praktijkvoorbeelden waarbij dit al toegepast wordt.
M7	<ul style="list-style-type: none"> <li>• Er wordt bij het product op meerdere vlakken naar veiligheid gekeken, bijvoorbeeld naar allergeniciteit, peptide-scanning. Er worden ook geen antibiotica markers gebruikt.</li> </ul>
<p><i>Welke (bedrijfseconomische) effecten heeft de Europese regelgeving op uw bedrijf? (Bijv. In hoeverre beïnvloedt de Europese regelgeving omtrent GGO's van de EU jullie concurrentiepositie wereldwijd?)</i></p>	
M7	De huidige wetgeving weerhoudt ons er van om de technieken toe te passen voor commerciële doeleinden en dwingt ons om traditionele mutagenese methodes te hanteren die minder snel en minder precies zijn. Wetgeving zou gebaseerd moeten zijn op wetenschappelijke argumenten, proportioneel en voorspelbaar. Momenteel is niet uit te leggen dat een product verkregen met traditionele mutagenese intrinsiek veilig is, maar dat een product verkregen met moderne mutagenese extra veiligheidsgoedkeuring moet ondergaan.

### A3.3.5 Regulatory Aspects

<p><i>Q: When looking at the international perspective, what are your main concerns related to the upcoming application of NBTs in microbiology ? What do you see as the major issues in this respect? Specific examples?</i></p>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>
M6	hindernis is: het opstellen en goedkeuren van nieuwe EU regelgeving.
M7	
<p><i>Q: Do you believe that harmonisation of regulatory requirements is important in this respect? Specific examples to underpin your conviction?</i></p>	
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<i>*niet specifiek behandeld*</i>
M5	<i>*niet specifiek behandeld*</i>

M6	Zowel in het algemeen als voor mijn bedrijf is internationale harmonisatie van de regelgeving van belang. Een bedrijf met een internationale markt moet rekening houden met alle lokale regelgevingen bij markt introductie van producten. Hoe meer die op elkaar afgestemd zijn, hoe duidelijker en hoe makkelijker dit in de productontwikkeling in te passen is. Als een belangrijke markt afwijkt en stringenter regels hanteert, zie je dat die indirect ook aan de andere regio's opgelegd worden. Tenzij de markt groot genoeg is om diversificatie in ontwikkelingstrajecten te verantwoorden.
M7	<i>*niet specifiek behandeld*</i> <i>Q: What would be your preferred route of harmonising regulatory requirements? Who should take the initiative to come to harmonised requirements? Would you be willing to participate in meetings on harmonisation (should these be organised at some stage)?</i>
M1	<i>*niet specifiek behandeld*</i>
M2	<i>*niet specifiek behandeld*</i>
M3	<i>*niet specifiek behandeld*</i>
M4	<ul style="list-style-type: none"> <li>• historie van veilig gebruik: zwaar laten meewegen</li> <li>• melkzuurbacteriën en bakkersgist – principe van equivalentie. De mensheid is al zolang bezig bewust en onbewust het genoom door elkaar te husselen</li> <li>• Selfcloning: zou vrijgegeven moeten worden. Niet het inbrengen van heterologe sequenties; dat zou men per product moeten bekijken</li> <li>• eerst de pijlen richten op de werkpaarden van de industrie. Laten we ons het leven een stuk eenvoudiger maken</li> <li>• zelfs bij gebruik van QPS organismen moet je op het moment dat je CRISPR-Cas toepast nog steeds veel informatie moet aanleveren.</li> <li>• Case-by-case bekijken naar veiligheid, liefst product-gebaseerd op een rationele manier.</li> </ul>
M5	<ul style="list-style-type: none"> <li>• een voortrekkersrol voor Europa is mogelijk, zodat andere regio's gaan volgen (Zuid-Amerika en Azië)</li> <li>• niet eerst wereldwijd overeenstemming, maar eerst binnen de EU, eerst tot een geharmoniseerde regelgeving. Kan een trigger zijn voor andere regio's, die zullen volgen</li> <li>• Je ziet een verschil tussen landen al in Europa. Noemt Frankrijk -traditionele landbouw is belangrijk.</li> <li>• De race in Europa is nog niet gelopen.</li> </ul>
M6	Dat weet ik niet precies. De EU zou hier bij betrokken moeten zijn. Aangezien de aanpak van de EU afwijkt van de meest gangbare aanpak bij andere grote economieën, zou harmoniseren ook al bereikt worden door de eigen regelgeving aan te passen. Internationale allianties geven wellicht het beste eindresultaat, maar duren te lang om af te wachten en kunnen op het allerlaatste moment alsnog gefrustreerd worden door een nationaal veto.
M7	<ul style="list-style-type: none"> <li>• Er moet duidelijkheid worden gecreëerd over de verschillende regelgevingen bij de kleine bedrijven. Grote bedrijven weten vaak wel de details.</li> <li>• Harmoniseren EU regelgeving, wellicht platform creëren voor bedrijven om dit onderwerp te bediscussieren</li> </ul>
	<i>Additional comments</i>
M5	<p>Huidige synthetische toolbox laten dingen toe die tot dusver niet mogelijk maken</p> <ul style="list-style-type: none"> <li>• vanuit duurzaamheidsoogpunt is dat goed</li> <li>• bijvoorbeeld voor de productie van stavia en biofuels dor GGO's zijn complexe engineeringapproaches nodig die alleen kunnen met de nieuwe toolbox</li> <li>• producten maken mbv minder energie en die een minder CO2 footprint hebben – dat kan alleen mbv moderne technologie</li> <li>• over 30 -50 jaar hebben we deze toolbox nodig</li> <li>• regelgeving houdt deze toepassing tegen</li> <li>• de samenleving en economie moet af moet van de olie. Voor biobased oplossingen heb je een efficiënte technologie nodig</li> </ul>
M7	<ol style="list-style-type: none"> <li>1) Waar moet nieuw novel food product aan voldoen? Het is een grijs gebied bij EFSA. Er zijn veel zaken nodig voor het samenstellen van het dossier. Vooral het allergeniciteitsdeel is belangrijk, maar EFSA geeft weinig informatie over hoe het te onderzoeken. Wel goede guidance in GMO documentatie FAO/WHO (2001, Evaluation of Allergenicity of Genetically Modified Food). Het is een lastig proces en wellicht houdt het bedrijven tegen. Een meer pragmatische aanpak zou kunnen helpen. Nu heeft EFSA een scala aan documentatie wat het lastig maakt voor kleine bedrijven om uit te zoeken. En daarbij, veel experimenten zijn erg kostbaar om uit te voeren (bijvoorbeeld de allergeniciteitstesten).</li> <li>2) Ontwikkeling RTDS technologie in VS: aangemeld als non-GMO techniek. Het wordt in de EU als GMO techniek gezien.</li> <li>3) Tweedeling in de wereld qua regelgeving, op basis van veiligheid voor mens/milieu maar ook economische belangen.</li> <li>4) Het samenstellen van dossier GMO schimmels is lastig, bijvoorbeeld plaats van random insertie, potentieel activeren silent genes en aantonen dat dit veilig is. Het is een arbeidsintensief proces. Terwijl filamenteuze schimmels (Trichoderma, Aspergillus, etc.) al jaren worden gebruikt.</li> <li>5) Er is behoefte aan praktische informatie bij het indienen van novel food dossiers, bijvoorbeeld informatie van andere bedrijven. Hoe hebben zij dit ingediend? En welke voor feedback hebben zij ontvangen? Zijn er topic-</li> </ol>

specifieke consultatiebureaus? Uitwisseling van informatie tussen bedrijven zou handig zijn.

6) Er zou evidence-based naar de regelgeving moeten worden gekeken, wat in de politiek vaak niet gebeurt.

7) Met CRISPR-Cas zouden modificaties sneller en preciezer kunnen worden gemaakt, in vergelijking met traditionele random mutagenese

## A3.4 Social Sciences Interviews

### A3.4.1 Perception

**Q1** Which trends do you observe in the public perception of modern biotechnology For example, has there been a decline or increase in public acceptance?

**S1** Geen sporen? Dan is er geen misdrijf en evenmin regulering mogelijk.

Na BSE crisis is voedsel kritisch op de kaart gekomen

· Sociale dynamiek, o.a. rond Hofuitspraak:

o Onhandige timing, § Echter, NGO's zijn stil geworden nu

o Grote groep is niet geïnteresseerd terwijl de rest gepolariseerd is Consumenten trends en perceptie

Positief over Bertolli (traditioneel imago voedselbereiding) en tegelijk ook over 'functionele' voedingsmiddelen

§ Lijken tegenstrijdig; Idem, perceptie van 'protein foods' als natuurlijk

o Bij voordeel voor de consument is er geen protesto

Keuzevrijheid belangrijk

o Twijfels ook onder juristen e.d. over huidige benadering regelgeving

o Verongelijkte houding wetenschappers

o Patriarchale houding leidt tot onrust

· Houding tegenover de verschillende toepassingen van biotechnologie

o Voeding: romantisch, gentech niet nodig

o Farmacie: wantrouwen tegen motieven van bedrijven

o Industrieel: onbekend hiermee en ongeïnteresseerd

**S2** \*Niet specifiek behandeld\*

**S3** Een algemene trend zie ik niet, wel dat verschillende incidenten of ontwikkelingen (tijdelijk) een effect hebben.

Bijvoorbeeld door Corona, wordt anders tegen synthetische biotechnologie aangekeken. In de maatschappij zie je nu met name een gepolariseerd beeld: een deel van de bevolking (erg) voor, en ander deel juist heel tegen. In de jaren 70 en 80 was er veel weerstand in de maatschappij gekomen; in Europa zijn de regels heel streng geworden, gebaseerd op het voorzorgsprincipe. Bij bepaalde incidenten komt de discussie, na een bedaarperiode, weer op gang, bijvoorbeeld toen er met CRISPR-cas baby's gemaakt werden en na de uitspraak van het Hof van Justitie van de EU over mutagenese (de uitspraak dat CRISPR wel als GMO wordt ingeschaald). Algemene beeld: heel verdeelde visies in de maatschappij, en meer gepolariseerde beelden. Je ziet wel veel verschillen in acceptatie tussen groene, witte en rode biotech, van blauw ben ik niet goed op de hoogte. Drastische gevolgen voor milieu zijn mijns inziens niet erg relevant bij witte biotech, door contained use en omdat eindproducten vaak geen GMO fragmenten meer bevatten. Ook is men er niet zo zeer mee bezig, het publiek weet weinig van de ontwikkelingen waar bijv. DSM mee bezig is. Als je breder publiek zoekt, komen er vaak juist degene op af die al geïnteresseerd waren. Ik ben wel een voorstander van openheid mbt biotechnologie en het publiek.

Is er een andere manier om publiek te bereiken? Een overstroming informatie, kan argwaan wekken bij de consument bij waarde-conflicten. Bijvoorbeeld als de Nederlandse overheid een pro-biotech zou uitzenden, kunnen consumenten juist gaan afvragen waarom dat nodig is, en wat daar achter zit. Voor educatie zijn dus juist vertrouwde bronnen belangrijk

achterdocht die leeft bij consument? Ja, in ieder geval bij een deel van het publiek. Info verspreiden gaat nu heel makkelijk via social media bijv. op Facebook. Op zulke platform leeft veel achterdocht, bijv. naar allerlei technologieën, biotech maar ook 5G, maar ook naar de politiek

**S4** We have to understand what concerns are about: what are underpinning reasons for public scepticism towards GMO's and other techniques. In particular amongst the European public, but also elsewhere, we see ambivalence towards the technology, which comes from the overarching dynamics, including the following wider questions:

- Why is it done/ why is a technology used? (Is it for a good reason?)

- Can we trust the scientists and regulators involved as honest brokers?

- What are consequences for stakeholders and ethics? Are the stakes understood?

Discussions on regulations provide a reduced sphere for interaction since they have been largely reduced to questions on technical risks, a part that provides little space for negotiation. In different jurisdictions we saw: molecular biologists have to answer different questions that they are poorly equipped to answer (effects on farmers, are you allowed to instrumentalized nature)



	With a new set of techniques (CRISPR-Cas, other forms of gene editing), there are a lot of same issues as before; I see no clear increase or decrease of public acceptance.
S5	<p>Trends:</p> <ul style="list-style-type: none"> <li>o Opinieonderzoeken o.a. COGEM</li> <li>o Geen trends, gevarieerd beeld</li> </ul>
Q2	<p>What are the determining factors for this perception of biotechnology?</p> <ul style="list-style-type: none"> <li>o For example, can these factors be related to attributes of the genetic modification process or the product, or to both? · § Example: recombinant DNA being 'unnatural' and therefore perceived as risky</li> </ul>
S1	<ul style="list-style-type: none"> <li>· Vrees voor misbruik door toegankelijkheid</li> <li>o Perceptie dat nieuwe technieken 'op de keukentafel' kunnen worden toegepast</li> <li>o Techno-optimisme versus voorzorg § Voorbeeld vuurwapen: combinatie kwaadwillende lieden en toegang</li> </ul>
S2	x
S3	<p>In de perceptie is heel belangrijk wat 'onnatuurlijk' is, of als onnatuurlijk klinkt of ervaren wordt. De associaties daarbij is onnatuurlijk = slecht (in tegenstelling tot bijvoorbeeld een bril of contactlenzen, die eigenlijk ook onnatuurlijk zijn).</p> <p>Ik vind dat een heel interessante associatie. Ook al zijn er hele precieze veranderingen mogelijk bijv met CRISPR cas, en treden er in de natuur heel veel modificaties, die afkeer blijft.</p> <p>Een zelfde afkeer voor onnatuurlijk zie je in E-nummers in eten.</p>
S4	<p>Does the way Europe approaches new inventions (according to the precautionary principle) give NGO's etc some room for opposing new techniques? Different than f e in VS, where substantial equivalence is the basis</p> <p>True, but there is another dynamic (underpinning reason why there is scepticism)</p> <p>Only partially explained by unknown risks and unknown unknowns. Another aspect is the way the new technologies transform agriculture, such as intensification; people are uneasy about that. The question is will techniques feed undesired practices? Besides there is the question: who will use a new technology, and who will benefit?</p> <p>Risks are discussed most, but the wider aspects are not so much addressed, even though they are there as well.</p> <p>German government: had stakeholder meetings on gene editing. A very harsh judgement was the result: Gene editing = GMO.</p> <p>People do not feel there is a proper process in place to regulate new technology. To solve the issue: this hard judgement of gene editing = GMO, so it is regulated for sure.</p> <p>It is the same for all difficult and complex agricultural developments and innovations. There is a general ambivalence towards the food system.</p> <p>University can say: "we have good reasons for an innovation as it will help solve grand challenges, so we need to convince the public", but will people believe it?</p> <p>In case of gene editing: some technical 'wizarding' may lead to a situation where edits do not have to be controlled – but is that desirable for the general opinion? The public does not wish to give away control</p>
S5	<ul style="list-style-type: none"> <li>o Positiever op medisch (noodzaak, positief effect van COVID, echter precair), in tegenstelling tot voedsel -Uitstraling naar andere (niet-medische toepassingen)? Nog niet gezien</li> <li>o Geen onderscheid tussen technieken, maar kleine veranderingen worden minder erg gevonden</li> </ul>
Q3	<p>What role does safety play in this?</p> <p>In addition, what is the trust in the safeguarding of and reassurance over safety by the authorities and legislators?</p>
S1	*Niet specifiek behandeld*
S2	*Niet specifiek behandeld*
S3	<p>Mensen hebben veel vertrouwen in natuurlijke producten en daar is vraag naar. Biotechnologie en producten daarvan worden als onnatuurlijk gezien, en daarom meer vragen over veiligheid.</p> <p>: Bijvoorbeeld cosmetica uit een (gemodificeerde) gist, is daar markt voor?</p> <p>Lastig, ethisch zou dat te prefereren zijn, maar mensen kunnen wat hypocriet zijn. Er zijn producten van DSM die op bijval rekenen kunnen, bijvoorbeeld als je er dierenleed mee kan voorkomen (Insuline, enzymen uit kalvermaag). Er zijn echter ook voorbeelden waarbij positief maatschappelijk effect niet gewaardeerd word, ik snap soms niet helemaal hoe het werkt: Bij Evolva's vanillesmaakstof gemaakt met synthetische biologie is er een hele rel ontstaan.</p> <p>: Omtrent witte biotech leven minder zorgen, zou dat blijven? Bij medicijnen en medische toepassingen is er meer acceptatie, op de Europese markt zijn medicijnen uit Amerika, die daar geproduceerd worden in genetische gemodificeerde geiten.</p> <p>Een deel van de perceptie en acceptatie van rode en groene biotech komt mogelijk door het moment waarmee je er mee in aanraking komt. Voor rode biotech: kom je mee in aanraking als je ziek bent en ben je geneigd de risico's te accepteren, terwijl je altijd met groene biotech te maken hebt ook als je gezond bent en dus niet de risico's hoeft te accepteren. De baseline is anders, en risico's zijn meer geaccepteerd als je al ziek bent. De consument en diens perceptie is erg belangrijk, die beslist met portemonnee en invloed op beleid.</p>

S4	<p>Norwegians: said disaggregate gene editing into: -technical (level) aspects -likely contributions to society and sustainability There may be a lot of promises, that need to be deliberated upon. Deliberation and those who deliberate matter: different disciplines should be involved in discussion and judgements.</p> <p>Not just experts that tell policy makers what to do, but there should be linking to public. Public dialogue should be wider than civil society groups.</p> <p>Yellow box: German government: had stakeholder meetings on gene editing. A very harsh judgement was the result: Gene editing = GMO.</p> <p>People do not feel there is a proper process in place to regulate new technology. To solve the issue: this hard judgement of gene editing = GMO, so it is regulated for sure.</p> <p>It is the same for all difficult and complex agricultural developments and innovations. There is a general ambivalence towards the food system.</p> <p>University can say: "we have good reasons for an innovation as it will help solve grand challenges, so we need to convince the public", but will people believe it?</p> <p>In case of gene editing: some technical 'wizarding' may lead to a situation where edits do not have to be controlled – but is that desirable for the general opinion? The public does not wish to give away control</p>
S5	<ul style="list-style-type: none"> <li>o Gevarieerd: <ul style="list-style-type: none"> <li>▪ Ingrijpen is 'not done' versus natuurlijkheid <ul style="list-style-type: none"> <li>• COGEM inventarisatie</li> <li>• Natuurlijke mutatie inbrengen wordt nog steeds als ingrijpen gezien</li> <li>• Intuïtief: veilig is niet gelijk aan gezond</li> <li>• Geen of weinig associaties bij het grote publiek</li> </ul> </li> </ul> </li> <li>o Vertrouwen in instanties is bepalend <ul style="list-style-type: none"> <li>▪ Veel mensen vertrouwen op de overheid</li> <li>▪ Echter, grote impact bij o.a. fouten</li> </ul> </li> </ul>

#### A3.4.2 Role of social sciences

Q	Role of echics: what roles do you see, including new ones?
S1	<ul style="list-style-type: none"> <li>o Autonomie om zelf afweging te kunnen maken <ul style="list-style-type: none"> <li>-Etisch matrix (voor en nadelen verdelen)</li> <li>-Niet-gelabeld met gelabeld mixen levert geen voordeel op</li> </ul> </li> </ul> <p>Voedselpiramide (oa keuzes bij welvaar): dierenwelzijn en duurzaamheid ook als belangrijke argumenten</p>
S2	*Niet specifiek behandeld*
S3	<p>Ethische beoordeling, gevoel speelt mee bij veel mensen en is een belangrijk argument om voor of tegen een techniek te zijn. Bij dieren is dit lastig: hoe zwaar weegt dierenwelzijn op tegen de onnatuurlijkheid van een biotechnologische uitvinding? In plaats van zo'n uitvinding zou je ook het probleem al bij de bron kunnen aanpakken door na te gaan wat de aanleiding is. Zaken die wel toelaatbaar lijken zijn GM kuikens waarvan het geslacht al in het ei kan bepaald worden terwijl ze nog niet levensvatbaar zijn (voorkomt vernietiging 1-dags kuikens). Ook diagnostica voor o.a. infectieziektes zoals COVID-19 zijn acceptabel als aan randvoorwaarden is voldaan. (uitleg: NLD heeft een 'nee tenzij' beleid voor biotech in dieren)</p>
S4	*Niet specifiek behandeld*
S5	<ul style="list-style-type: none"> <li>• Ethiek: geeft inzicht in zorgen e.d. die leven, maar geeft geen antwoord</li> <li>• Voorbeeld: vrijstelling van medische toepassingen van GM dieren</li> <li>• Input voor de politieke discussie?</li> <li>• Geen optelsom, maar wel basis voor besluit</li> </ul>
Q	To what extent what extent are participatory methods applicable, e.g. consensus conferences, to decide on a shift in legislation?
S1	<ul style="list-style-type: none"> <li>o Veel te halen hieruit, maar: <ul style="list-style-type: none"> <li>-Tijdslijn?</li> <li>-Dynamiek</li> <li>-Voldoende realistische zaken om te bespreken nodig terwijl toch nog bijsturing mogelijk zou moeten zijn</li> <li>-Representatieve vertegenwoordigers die deelnemen hieraan?</li> </ul> </li> </ul>
S2	*Niet specifiek behandeld*
S3	<p>Yellow box: Consensus conference: doorsnee van de bevolking, kijken of je met groep willekeur geselecteerde deelnemers tot een overeenstemming kunt komen. Wordt bijvoorbeeld in Denemarken gedaan.</p> <p>Uit een consensus conference komen vaak heel interessante inzichten voort. Praktisch gezien is het lastig, hoe zorg je dat je randomisatie van deelnemers hebt, Hoe leg je begrijpelijk uit wat er aan de hand is. Daarnaast spelen er in politiek ook andere belangen(economisch, handel), die kunnen niet in zo'n consensus conference moeilijk meegewogen worden.</p>

- S4 Deliberative aspect is very important; and the way that people can develop their own viewpoint within groups. Surveys and social media are useless in this regard. In my work, I prefer to work with focus groups. For consensus conferences, the question asked is very important. "Should we have a product- or process-based approach?" would be a bad question for a consensus conference as lots of assumptions may not be shared. You need to have a prior process about what the right framing of a question is.
- When is something a legitimate concerns – DEBATE between EU and VS**  
Is it legitimate to raise questions about environmental health risks.

- S5
- Participatieve methoden, o.a. consensus conferenties
    - Zijn tijdelijk populair geweest
      - Afwijkende meningen vielen buiten de consensus
        - [voorbeeld: GRACE stakeholders]
      - Over dit onderwerp is er geen consensus, niet iedereen zit op 1 lijn
      - Vaak is er een beperkte rol van de participatie in de besluitvorming
        - Verwachtingenmanagement nodig
        - Vaak teleurstellend voor de deelnemers

### A4.3.3 Policy

**Q1 Precautionary principle: How is the principle affected by a transition from process- to product-based legislation?**

S1 \*Niet specifiek behandeld\*

- S2
- Background:
    - Cross-cutting for EU legislation
      - § Primary principle
      - § Not limited to a particular sector
  - No general interpretation of the precautionary principle
  - Interpreted slightly differently between sectors; Exception: defined in the GFL (2002) art 7: consumer
  - Aims: Protection of public health and the environment safety is put as a priority before the internal market
  - Cited by the Court of Justice of the EU (court case) and the GMO Directive
  - Science at the heart of it, although labelled as anti-scientific by adversaries
  - As described in the European Commission's communication from 2000
  - Any authorization/withdrawal from market has to be based on objective science
  - Precautionary principle applies when there is an unknown risk

S3 Ik zie nu dat het precautionary principle vooral belemmerend werkt in de EU. Het precautionary principle impliceert dat we ons zorgen moeten maken over nieuwe technologieën. Dit heeft veel invloed op Europa, en hoe Europa daar tegenaan kijkt (mn NL en noord Europese perceptie) Of het vertrouwen in politiek, wat in Zuid Europa heel anders is, daar invloed op heeft weet ik niet. Ook in Nederland zijn er sceptici van het beleid.

S4 See Q1 perception

- S5
- Voorzorgsprincipe: referentie aan de Europese Commissie 2002/3
    - Interpretatie: maatregelen nemen met betrekking tot nieuwe technieken maar wel zo spoedig mogelijk onzekerheden wegnemen
      - Perpetuum mobile
        - Science-based/voorzorg wel genoeg? Dit is een politiek besluit
      - De EU benadering is precautious
        - Vrijstellen op basis van zekerheden
          - Nog steeds uit voorzorg handelend
        - Geen proactieve actie om onzekerheden weg te nemen

**Q2 Innovation: How will it be impacted by such a transition from process- to product-based legislation? Which innovations might be boosted or thwarted?**

- S1
- 'Proces-gebaseerd', argumenten in het voordeel hiervan:
    - Wantrouwen bij verborgenheid
    - 'onontploft rotje'

S2

Dependent on final proposal for new regulation and the way it is phrased

-As is general law, no new proposal will escape the precautionary principle

-Farm-to-fork considerations important for safety assurance too

-'No proof it's safe' arguments from certain organizations in society

Precautionary principle addresses unknown risks

-Surprising if not in new law, is already in primary treaties

Other directive from 2015: possibility for memberstates to opt out from cultivation for other than scientific reasons

-Example of memberstates previously invoking scientific arguments to underpin national bans



	<p>-No need anymore to disprove safety as sole trigger for a ban</p> <p>-Interesting observation: no court cases against member states so far on this issue</p> <p>-Even with new regulation, memberstates will use a similar technique to ban these products (referring to directive from 2015) - resistance expected, concern amongst consumer organizations: precautionary principle might not be in new law</p> <p>Problem: fragmented market</p>
S3	<p>Moeilijk om te voorspellen. Dat hangt of witte biotech dan niet meer onder GM valt? En Zou daar dan minder onderzoek naar zijn? Nu geldt al voor sommige eindproducten (additieven e.d.) waar geen GM eiwit en DNA in is dat er niet een aparte toelating als GM nodig is.</p> <p>RISICOASSESSMENT bij de organisaties terecht gekomen, en dat is heel veel werk geworden. In Delft hebben we een platform moeten ontwikkelen omdat er geen tools of leidraad beschikbaar was. Dat heeft veel werk gekost – terwijl er mogelijk op andere plekken ook aan gewerkt is. Vergunningsaanvragen, veel papierwerk! Een groot deel van het werk komt bij BSO's (=biological safety officers = bioveiligheidsfunctionaris) te liggen.</p> <p>Op de universiteit zijn we vaak niet met producten bezig, maar juist naar heel algemeen onderzoek naar technologieën. Eindtoepassingen en eindproducten leven vaak minder, al komt er soms uit samenwerking of uit een eerder onderzoek een meer toegepast onderzoek voort.</p> <p>Wat zou dat betekenen, wat definieer je als product ?</p> <p>■ aantonen wat je mutatie al van nature voorkomt of al eerder gebruikt is?</p> <p>Nu worden gegevens ook al aan onderzoekers gevraagd en moet vaak extra info aangeleverd worden. Als dat sneller of flexibeler gedaan wordt is er winst te boeken. Nu moet een onderzoeker in ML III lab aantonen dat iets veilig is, dat er ook in een ML II lab mee gewerkt kan worden. Maar MLIII labs zijn schaars – dus hier is verbetering mogelijk.</p> <p>Er lopen nu een aantal projecten die kijken naar (sporen van) DNA en eiwitten die mogelijk in afvalwater en na autoclaveren aanwezig zijn. Zou dit alsnog een risico opleveren terwijl het commerciële eindproduct deze zaken niet meer bevat? (uitleg: nationaal toezicht gesloten faciliteiten)</p>
S4	<p>■ : <i>Example of mobile phones: in the beginning there was fear of brain tumours But now all gone Benefits may have overshadowed the original fears</i></p> <p>The promise was that cell phones would be wonderful, and everybody bought into this and into Google, Facebook etc.; this held true for customers but also people within policy circles.</p> <p>Now we found out: big tech has very complicated effects on society. Big tech has enormous power, and that raises all kinds of concerns. The current situation raises all new questions on parenting and responsibility for example. It also has fostered polarization within civil society, bypassing political arrangements.</p> <p>Governments are struggling how to deal with changes in social life due to (revolutionizing) technology. They struggle with negative side effects and the questions what is collective responsibility.</p> <p>To mitigate effects before they occurred, another type of assessment of technology needed. Technologies do transform life. If a new technology like gene editing, it as powerful as we expect, than we should think about effects in advance. For GM we could not think it through, so it was banned.</p> <p>Populism – new techniques used for their own success, and have a very wide impact on the world. That impact can be negative, the situation with Cambridge analytics is an example.</p> <p>■ : Powerful technology: is legislation a tool to steer it in the right direction?</p> <p>You got to have some regulation as well.</p> <p>The questions: what is likely to be seen as most credible and legitimate</p> <p>You have to engage with 'lay ethics'. Technology is transforming ethical categories itself; we are dealing with very complicated dynamics right now.</p>
S5	*Niet specifiek behandeld*
Q3	Sectors (Agro, Pharma, Industrial): To what extent can different approaches be followed for different sectors?
S1	*Niet specifiek behandeld*
S2	*Niet specifiek behandeld*
S3	<p>■ (op basis van discussie hierboven) Deze issue leeft misschien niet direct in Witte biotech, komt meer uit de plantensector!</p>
S4	<p>Xx ■ <i>During the CRISPR con conference: an example of a patient with heritable disease discussed: patient had no normal life, huge costs for society Completely different perspective than use in plants; perhaps applications in production animals are most contested</i> I think the use of gene editing is very contentious in plants and microbes as well, both societal and political. Discussion should engage with wider dynamics; medical use of editing techniques is very different from editing a mushroom. What are the foreseen and unforeseen effects? Engage with the dynamics!</p> <p>Example on GM in plants in late '90's and early in 2000, a lot of publications came out on positive effects GMO's could have. The developments were mainly in herbicide and insect resistant crops, not really GMO's to help developing societies in Africa. The promises of new techniques have to be seen as credible; it depends on who funds research and who defines problems for these promises to be found credible by the public. Otherwise people will get cagey, asking: Who? What for?</p> <p>Example of Gene drives: there has been some debate there, such as on gene drives for conservation, and for</p>

malaria control. Lots of questions about the technique, including is introduction reversible. If you meddle in biological process by intervening in nature, then the public view will be that nature will 'fight back'. You can't think you have all bases covered. It needs to be thought through.

- S5
- Onderscheid tussen dier, plant en micro-organisme
    - O.a. in Nederland gedifferentieerd voor o.a. GM proefdieren
      - Dieren: 'aibaar'
      - In praktijk lastig voor verschillende dieren
      - Lastig voor wetgeving om bescherming af te bakenen

#### A4.3.4 Legislation

**Q** What regulatory foundation do you envisage for a product-based legislation? . For example, would an extension of the 'novel foods' legislation be possible?

S1 \*Niet specifiek behandeld\*

S2 Confederation case:

- Judges' challenge: Whose science do you believe?
- Problem: New breeding techniques are novel technologies with unknown risks
- Science is untested. You cannot prove it to be safe yet.
- Reason for deadlock
- CJEU Court decision has raised the question what is meant by 'conventional'?
- Conventional = considered safe
- Scientists: nothing conventional about radiation and chemical mutagenesis § These are actually also artificial, § Hazard/risks are known.
- The court looked more at the precautionary principle
- Judges needed to interpret law as it was, yet it was also recognized that law is still evolving
- Exemption of conventional mutagenesis used before 2001:
- § The court looked at it from a consumer protection perspective, not an innovation perspective.
- Reason for disappointment of, for example product developers: Gene-edited crops would have to go through risk assessment:
- § Subject to moratoria (at policy level)

S3 \*Niet specifiek behandeld\*

S4 \*Niet specifiek behandeld\*

- S5
- Voorbeeld Canadees model:
    - In hoeverre levert vrijstelling van 'niet-novel', producten op als deze niet innovatief zijn?
    - 'Novel' is niet goed gedefinieerd
      - Bijvoorbeeld: significante verhoging metaboliet
    - Contact met overheid van ontwikkelaars
    - Verschillende benaderingen voor andere sectoren
      - In Canada minder georganiseerd dan voor EU
        - In Canada is onderlinge afstemming beter
    - Extra stemronde in de EU (politiek) is een verschil met Canada
  - Juridische basis zoals voor novel foods?
    - Geïnterviewde geeft aan geen jurist te zijn
    - In Canada wordt dit ook voor planten gedaan
      - Verder uitwerken voor anderen

**Q** To what extent is alignment with legislation of other countries needed?

S1 \*Niet specifiek behandeld\*

S2 Legislation elsewhere (eg Northern America/ Argentina)

- § Reputed for being less rigorous
- § Divergence (from the EU) in interpretation and application of the precautionary principle and risks
- § Easier for the authorization to go through
- § CRISPR-Cas is commercialized in the US. But Europe is not certain about it
- There is a difference in the approach of risk and risk perception

Resistance against GMOs overall, as well as New Breeding Techniques in particular

- § Unsure if this can be overcome
- § Potential political decision is influenced by public acceptance

S3 Er zijn nogal wat verschillen tussen regio's wereldwijd, in Zuid Amerika is men juist heel positief, wordt met trots geadverteerd op producten dat het met biotech gemaakt is. Dit is ook wel weer vergaand –ik ben in principe Geen tegenstander van precautionary principle, maar oppassen dat het innovatie remt. Als EU wil je ook niet dat alle



	biotech naar andere werelddelen gaan. Om te leren over risico's moet je nieuwe technieken wel gebruiken, in een delicate balans met het streven om onnodige risico's te mijden
S4	*Niet specifiek behandeld*
S5	<ul style="list-style-type: none"> <li>• Harmonisatie met andere landen? <ul style="list-style-type: none"> <li>◦ Altijd mooi</li> <li>◦ Risicoanalyse werkt toch <ul style="list-style-type: none"> <li>▪ Probleem ligt meer bij de besluitvorming in de EU</li> </ul> </li> <li>◦ Internationaal: vrijstellingen, aanpassingen</li> </ul> </li> </ul>
Q	How much resilient will a new product-based legislation be as compared to a process-based one?
S1	<p>Regels: zorg dat het klopt!</p> <p>Voor de overheid:</p> <ul style="list-style-type: none"> <li>- Verantwoordelijkheid neerleggen bij anderen, minder geven.</li> </ul> <p>Sentiment, populistische argumenten</p> <p>-Ander voorbeeld waar dit werkt: voedsel etiketten</p>
S2	<p>Technology is very broad, not necessarily controversial in each case</p> <p>§ Challenge for regulators: Reconcile with concerns and ethics</p> <p>§ Not enough normative guidelines or principles that everyone can agree on</p> <p>§ Precautionary principle in EU: hated by the US, trying to weaken it</p> <p>§ CETA controversial because of food safety, e.g. GMOs</p> <p>§ US is patent friendly; quick from patent to product on the market, within 1 year (profit-driven)</p> <p>◦ US is aggressive on IP in trade negotiations</p> <p>◦ EU is patent friendly too, but often cannot commercialize the product</p> <p>◦ US see precautionary principle as hampering</p> <p>§ Regulatory convergence is controversial</p> <p>◦ Perception: Regulations in the EU are much better than in the US</p> <p>◦ Food is sticking point in negotiations</p> <p>§ Mention food products from NBTs already on the US market: CRISPR-Cas peanuts</p> <p>§ Mini-trade deal: one to watch. Might speed up the authorizations</p> <p>§ EU member states are not using the science deployed by EFSA anymore: Even if safe, they still bar market admission</p>
S3	*Niet specifiek behandeld*
S4	*Niet specifiek behandeld*
S5	<ul style="list-style-type: none"> <li>• Future proofing van wetgeving? <ul style="list-style-type: none"> <li>◦ Wetgeving nu in de knel, o.a. door verwijzing naar 'natuurlijk' (GGO definitie) <ul style="list-style-type: none"> <li>▪ Dit wordt gemedan bij gebruik van 'nieuw' <ul style="list-style-type: none"> <li>• Wel definitie hiervoor nodig</li> </ul> </li> </ul> </li> </ul> </li> </ul>
Q	At what timescale do you expect such a change from process- to product-based legislation to take place, if at all?
S1	• Internationaal: argwaan tussen lidstaten
S2	<p>§ Difficult to tell</p> <p>◦ If there is political consensus; can go quickly (within 2 years)</p> <p>§ Probably will take longer</p> <p>§ Would need to overcome resistance from e.g. France, Austria, Germany</p> <ul style="list-style-type: none"> <li>• So far, resistance has been felt</li> </ul> <p>◦ If it is a controversial issue facing opposition (consumer resistance), progress will be slow</p> <p>§ Compare with data protection legislation:</p> <ul style="list-style-type: none"> <li>• Lots of amendments</li> </ul> <p>§ Another example: biotech patents</p> <ul style="list-style-type: none"> <li>• Took more than 10 years to become established</li> <li>• Already outdated when introduced</li> </ul> <p>◦ Same for GMO Directive</p> <p>§ Will need to go through e.g. Council and EuroParliament</p> <p>◦ New green deal:</p> <p>§ Focus has shifted to green/sustainable agriculture with biotechnology</p> <p>◦ It could go either way</p> <p>◦ Can go quickly, but need consensus in the parliament.</p> <p>§ EPP in favour, yet Socialists may team up with Greens</p> <p>§ Juncker previously banked on competitiveness yet Von der Leyen is more into a Green Deal</p> <ul style="list-style-type: none"> <li>• No policy escapes</li> <li>• NBTs might be received as leeway to reaching Green Deal goals</li> </ul>

	o Would need everybody to line up and agree that 'This is the way!'
	o However, there might be pushback from other organizations that do not see the sustainability
S3	*Niet specifiek behandeld*
S4	*Niet specifiek behandeld*
S5	<ul style="list-style-type: none"> <li>Tijdsschaal: <ul style="list-style-type: none"> <li>Al lang bezig, sinds 2006, over nieuwe veredelings technieken (NBT's)</li> <li>5-10 jaar nodig voor aanpassingen <ul style="list-style-type: none"> <li>Het invoeren van uitzonderingen of vrijstellingen is gemakkelijker</li> <li>COVID: voorbeeld van drastische vrijstelling voor GGO proeven <ul style="list-style-type: none"> <li>Contrast met GGO planten</li> </ul> </li> </ul> </li> </ul> </li> </ul>
Additional comments	
S4	<p>What would a forward looking governance method look like?</p> <p>Instead of retrospective to future-oriented legislation.</p>
S4	<p>: During a previous workshop, the administrative procedures and their consequences were discussed</p> <p>S4: There is a lot of procrastination, and not being able to make up your mind in GMO, but the whole Dynamic in GMO made it like that. Whole system is discredited. It is important to have proper politics of innovation. Currently, politicians and political decisions will follow science, that does not work! A product-based legislation might make everything even worse</p>

### A4.3.5 Ethics

Q1	Are these proposed changes reconcilable with ethical principles? For example, would this not conflict with the Dutch stance on animal biotechnology (dismissive of animal biotech for the purpose of productivity increase)
S1	*Niet specifiek behandeld*
S2	*Niet specifiek behandeld*
S3	<p>Bij dieren meer naar de bron kijken van een probleem, bijv. intensieve veeteelt. Persoonlijk denk ik dat we binnen Europa niet heel netjes met dieren omgaan – bij de bron aanpakken van problemen, bijv door beter voer geven. Lijkt me in deze situatie beter.</p> <p>: Hoornloos rund fokken door gebruik maken van gene editing?</p> <p>Komen we weer bij natuurlijk / onnatuurlijk. Als je leed bespaart, zou dat acceptabel zijn. Echter omdat ze te dicht bij elkaar staan – dus daar blijft het een dilemma of dat met technologie moet.</p> <p>: Een ander voorbeeld uit de industrie: dmv modificatie haantjes in eieren kunnen opsporen, zodat deze vroegtijdig kunnen worden opgespoord? Deze toepassing zou ik acceptabel vinden als daar mee leed bespaart blijft. Ik denk dat voor mij levensvatbaarheid een rol speelt.</p>
S4	*Niet specifiek behandeld*
S5	<ul style="list-style-type: none"> <li>Ethiek: geeft inzicht in zorgen e.d. die leven, maar geeft geen antwoord <ul style="list-style-type: none"> <li>Voorbeeld: vrijstelling van medische toepassingen van GM dieren</li> <li>Input voor de politieke discussie?</li> </ul> </li> </ul> <p>Geen optelsom, maar wel basis voor besluit</p>
Q2	Is an ethical assessment still possible?
S1	<ul style="list-style-type: none"> <li>Risico: subjectieve ethische afweging <ul style="list-style-type: none"> <li>Filter op informatie, Beïnvloedt de 'denkraam'</li> <li>Techneuten onderkennen dit niet</li> <li>Inversie: Bescherming van baby's en ouderen wordt nagestreefd terwijl dit eigenlijk het meest voor studenten als kwetsbare categorie zou moeten gelden Onnatuurlijkheid (perceptie: riskant) versus daadwerkelijk risico</li> </ul> </li> </ul>
S2	*Niet specifiek behandeld*
S3	*Niet specifiek behandeld*
S4	<p>Talking to Dutch focus groups, there was a widely felt sentiment that for agriculture: you have to come up with a VERY good reason to justify editing, such as animal welfare. In the example of hornless cows, though, should you solve this issue by the use of gene editing, or could you instead change something in the housing or the living conditions? The same is valid for disease resistance.</p> <p>Framing is important, as the public may not accept frames. In the past: GMO work with Unilever. Unilever wanted to market GMOs positively! You cannot be sure you keep the narrative, or will it be framed as 'Franken foods'.</p>
S5	<ul style="list-style-type: none"> <li>Ethiek: geeft inzicht in zorgen e.d. die leven, maar geeft geen antwoord <ul style="list-style-type: none"> <li>Voorbeeld: vrijstelling van medische toepassingen van GM dieren</li> <li>Input voor de politieke discussie? <ul style="list-style-type: none"> <li>Geen optelsom, maar wel basis voor besluit</li> </ul> </li> </ul> </li> </ul>

### A4.3.6 Additional statements

S1	<ul style="list-style-type: none"><li>Generaties: verschillende benaderingen tegenover informatie en technologie<ul style="list-style-type: none"><li>Babyboomers, o.a. welvaarts'boom'</li><li>Generatie X: pessimisme</li><li>Millennials: Welvaart, computers, Internet</li><li>Generatie Z: o.a. klimaatdiscussie, Internet; § Kritisch over bronnen, tricky over overheid Willen weten hoe het gemaakt is, wantrouwig</li></ul></li></ul>
S1	<ul style="list-style-type: none"><li>Etikettering, nut:<ul style="list-style-type: none"><li>Authenticiteit</li><li>Tracking &amp; tracing (blockchain bij voldoende marge)</li></ul></li></ul>
s2	<p>Enforcement</p> <p>§ Authorities in the EU do indeed check for compliance with GMO regulations</p> <p>o Whether they are able to detect products from NBT: hard to say if the mutation detected is natural or artificial?</p> <p>§ Mutations happen slowly in nature</p> <ul style="list-style-type: none"><li>Surprising if suddenly became speedy (e.g. a whole seed lot)</li></ul>
S3	<p>■ Zie je verschil in acceptatie tussen generaties?</p> <p>In mijn perceptie zijn vorige generaties opener tegenover nieuwe technologieën dan huidige generaties. Bijvoorbeeld: Eten in blik, in poedervorm, gevriesdroogd; allemaal positief ontvangen. De huidige generatie is mijn inziens sceptischer tegenover innovaties met voedsel en eet bijvoorbeeld liefst biologisch terwijl dat niet altijd duurzaam hoeft te zijn; <i>idem</i> voor vleesvervangers op basis van soja: waar komt deze vandaan?.</p>
s4	<p>■ : painting a picture of gene editing as a powerful tool, is that damaging in your opinion?</p> <p>What is the truth of the matter? It is a way of engaging society in it.</p> <p>If you believe it is very powerful, you should think of a responsible way of using the technology and on the consequences.</p> <p>The pretence that the technology is nothing special is also a wrong approach</p>
S4	<p>■ : Are more fundamental changes needed than just changing regulations?</p> <p>Indeed I think so! Problem is that the system is mistrusted: what is the plausibility?. Distrust towards those who gets to frame the process and the questions. Previous processes have framed the methodologies; a bottom-up way is preferred over this top-down approach, though.</p>
S4	<p>Fundamental problem: we do not have politics of technology &amp; innovation.</p> <p>Historically: commonly assumed technology is good. (Should be used and permitted, unless there is a reason not to). In general, the market will decide if and how a technology develops. Reasons why technology should not be permitted can be environmental, health-related, or ethical.</p> <p>Questions of who is going to benefit, but who won't is important as well.</p> <p>At the moment we are not thinking it through in the right way. In innovation related to livestock farming: becomes a forum where these questions become more pertinent, as animals are sentient beings.</p> <p>In the focus groups, we discussed cases where gene editing could help with economical and sustainability issues.</p> <p>Dutch public responses: sticking a plaster on a wound. Does not look at fundamental questions of the food system.</p>
S4	<p>■ : Discussion: should be about what kind of agriculture do we want, that is, have a shared vision first and then select the appropriate tools to achieve it?. Important caveat: tools are never neutral, they have their own politics (e.g. motor cars leading to a new infrastructure, as well as nuclear power requiring specific security measures and governance). Thus only discussion and working on goals is not enough.</p> <p>■ : Where should discussion on the techniques? Parliament?</p> <p>Deliberative methods are important. My opinion: discussion in parliament can be quite limited, example of promoting UK science and synthetic biology. How to foster or develop debate in government and parliament is important. In this respect: my idea is that it is the Achilles' heel of the WUR that it is so promotional about novel technologies. University should not be a promoter of technology, but an honest broker, considering how the technology could fit in society.</p> <p>In this line, CRISPR Con was a mistake in my opinion: 'it is amazing, how do we get to everyone to support it.'</p> <p>I'm not saying scientists should be impartial, but they should be Reflective: should be involved in society.</p> <p>Dutch government has advantage: relatively consensus-focussed society('poldermodel'), a lot of trust in the government.</p>

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# Annex 4      Process-based versus product-based assessments of genetically modified plants, animals and micro-organisms

## Economic implications

5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e5.1.2 e

### A4.1      Introduction to Product and process based scenarios and their economic implications

Because agriculture is an important part of the Dutch economy any changes in regulation of novel GMOs, including gene-edited varieties, may have far-reaching economic consequences, both for the Netherlands and for other EU member states (Rikilt). The legislation of GMOs (now also including many NPBTs, see Purnhagen et al., 2019) were established more than 25 years ago. A clear distinction is made between the transgenic and conventional bred plants. In the Directive 2001/18/EC, both process- and product-based terms are included. However, the Directive is mainly interpreted as a process-based legislation. New techniques are emerging that are closer to conventional breeding and may be difficult to distinguish. It could therefore be beneficial to have a more product-based legislation. In this case, the resulting products are regulated instead of the production process and the debate about whether or not the end result is a GMO and what constitutes a GMO will be less relevant (Sprink, Eriksson, Schiemann & Hartung, 2016).

The current EU legislation towards new genetic engineering techniques gives uncertainty for both research institutes and private companies (Sprink et al., 2016; Purnhagen und Wesseler, 2019; Wesseler et al., 2019; Nationale Akademie der Wissenschaften Leopoldina, Deutsche Forschungsgemeinschaft und Union der deutschen Akademien der Wissenschaften. 2019.). Both public and private companies would therefore be hesitant to incorporate materials into breeding populations, even if the resulting plant, animal or microorganism would only have small deletions in endogenous genes or point mutations, if these plants would be regulated as being a GMO (Eriksson et al., 2018). Also, process-based regulations for GMOs are, in general, stricter compared to the product-based regulations. It therefore requires more time to obtain a regulatory approval (Araki & Ishii, 2015; Smart et al., 2017).

In case of process-based GMO regulations, GMOs have to undergo a regulatory review which involves a procedure that is based on scientific assessment of the (negative) effect it might have to human health and the environment. Besides the EU, e.g. Australia (Gene Technology Act 2000), China (Administrative Measures on the Safety of Import of Agricultural Genetically Modified Organisms 2017), Japan (Framework for application, approval, investigation, and utilization of genetically modified organisms based on the Cartagena Protocol) and New Zealand (Hazardous Substances and New Organisms Act 1996) have adopted process-based GMO regulations (Eriksson et al., 2019; Ebata et al., 2013; Jin et al., 2019). In case of product-based GMO regulations, these human health and environmental risks associated with a GMO are assessed based on the final product instead of the production process. This product-based approach is used in several countries, including the USA (7 CFR Part 340), Canada (Food and Drugs Act) and Argentina (National Biosafety Framework) (Araki & Ishii, 2015), although also in these countries there are clear process-based considerations to assess a product. Using a more product or process assessment can therefore make a big difference in regulation of new techniques. It is thus important to consider which approach is most beneficial for the regulation of GMOs (Van Bueren et al., 2007).

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#### A4.1.1 A process-based approach

The EU legislation on GMOs is process-based. A decision was made that required an environmental risk or food safety assessment for the GMOs. This decision is based on the production process of the organism instead of the end-product (COGEM, 2019).

There are four different situations we will further elaborate that could be used for the regulation of products where gene editing was used.

##### **Situation I: Process-based approach (current situation)**

Products developed by all novel breeding technologies (e.g. gene editing) are regulated according to the existing GMO regulatory framework. Products developed by radiation or chemical induced mutagenesis are exempted (Rikilt).

##### **Situation II: (Sub-scenario) Process-based approach**

Products developed by use of novel technologies that induce only small modifications or SNPs (that cannot be related to the use of modern mutagenesis techniques) are exempted (Rikilt).

#### A4.1.2 A product-based approach

A product-based approach for the safety assessment of GMOs is different from the process-based approach because the basis of this regulation is the characteristics of the end-products. The process used to obtain the product is not considered in this approach. This means that new techniques do not have to be assessed individually to determine whether or not additional safety assessments apply. Instead, if the EU were to use this approach for their GMO legislation, a new variety has first to be assessed if additional environmental and food safety tests will be needed. This would mean that some plant varieties that are currently regulated as a GMO by the EU might not require additional safety assessments anymore. On the other hand, some conventionally bred plants that currently do not fall under the environmental and food safety assessment applied to GMOs will have to be assessed. As a consequence, the product-based approach might encourage companies to use NPBTs or new techniques used for animals or micro-organisms more often because the crops that do not have significantly different traits than conventional bred crops would not require additional safety assessments. This could lead to an increase in crops that were produced using NPBTs. However, products or crops would still be regulated if they have new characteristics that are clearly different from the products or crops that are already on the market (COGEM, 2019).

##### **Situation III: Product based approach**

All products are (basically) assessed prior to entering the European market, comparable to the current Novel Foods approach where products that do not have a (confirmed) history of safe consumption may be assessed as novel foods products. Novel foods that are clearly different from products already on the market will require a pre-market safety assessment. There will be a grey area of products that may or may not be regarded as novel foods. It will need to be considered how to assess new plant/animal/microbial organisms for environmental safety (Rikilt).

##### **Situation IV: Product based approach**

An alternative approach for new plant varieties may be adherence to the UPOV regulations for new plant varieties and include safety aspects in the registration procedure. This may allow for global harmonisation of market approval of new plant varieties. It will need to be considered how to assess new animal and microbial organisms in a similar procedure (Rikilt).

These situations are both comparable to the current Novel Foods Regulation. GMOs can in this case be placed on the European Market after the applicant has submitted an application for authorization that is in line with this regulation. The Commission can decide to give authorization for placing on the market of the novel food. If the GMO might have effect on human health, a risk assessment will be carried out by the EFSA. Also, labelling is required as is laid down in Regulation (EC) No 1169/2011. In case of GMOs, additional requirements might apply to better inform the consumers about the products (European Commission, n.d.-b). If products that are derived from genetically modified organisms

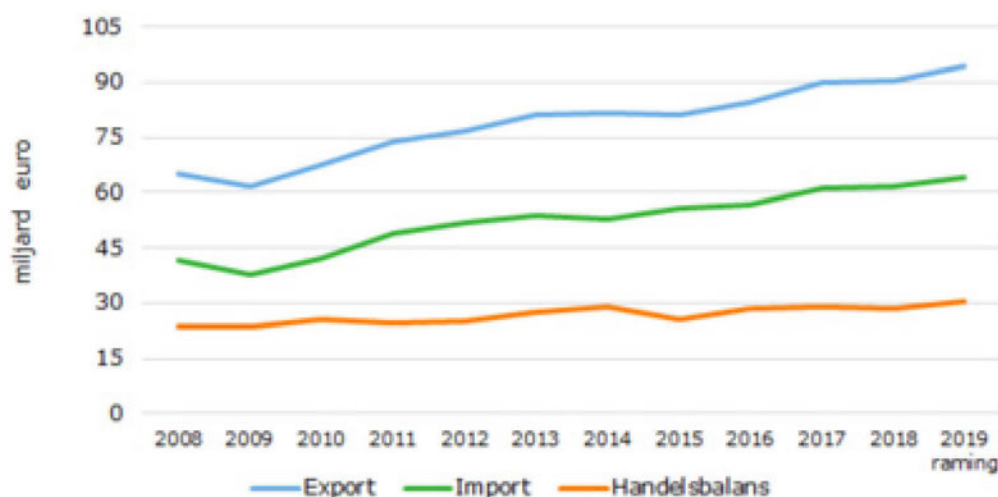
would be assessed according to the novel food regulation, this would be less time consuming as only the products that are clearly different from products already on the market need to undergo a pre-market safety assessment. Moreover, the authorization process will be shortened and simplified. This will reduce costs for producers both within Europe and for producers from outside Europe and the process for novel foods including GM derived food and feed will be clearer.

## A4.2 Plants

### A4.2.1 Economic importance plant breeding sector

Plant breeding is a highly important sector for the Dutch economy and economic perspectives.

Since 2009, the Dutch export has increased every year (see Figure 1). In 2019, the Dutch export of agricultural products increased again and reached an export of €94.5 billion worth of goods (see Figure 1). This export rate for 2019 shows that the agriculture and horticulture sectors in the Netherlands have a leading position in the world market (Ministry of Agriculture, Nature and Food Quality, 2020).



**Figure 1** Export, import and trade balance of agricultural goods; Source: CBS, WUR

When looking specifically at the seed breeding companies, the Netherlands has a leading position on the world market as well. For the biggest companies in the world that are processing vegetable seeds, eight out of ten have an office or headquarters located in the Netherlands (Kocsis, Weda & van der Noll, 2013). For the international trade in the horticulture sector, 40% of the seeds has its origin in the Netherlands. The percentage of international trade for the seeds of potatoes is even 60%. The Dutch seed companies have locations in more than a hundred countries, both in sales and in the production of the seed (Ministry of Economic Affairs, 2017). The Netherlands also has a partnership with various countries. This partnership stimulates Dutch companies to scale up their investments, also to be able to produce seeds that could be sold on the international market. Business continuity of the Dutch seed sector is dependent on innovation as seed companies spend on average 15% of their turnover on R&D. Some companies invest even nearly 30% to guarantee the improvement of varieties and seed quality (Ministry of Economic Affairs, 2017). As can be seen in Table 1, the biggest companies in the seed breeding sector in the Netherlands have almost doubled their export value in the period from 2010 till 2017.



**Table 1** Seed breeding companies with more than 100 employees

Year	Number of companies	Amount of jobs	Export value (mln euros)
2010	10	3010	688
2011	10	3550	867
2012	10	3690	991
2013	10	3810	977
2014	10	3930	1028
2015	10	3930	1065
2016	10	3910	1140
2017	10	4000	1265

Source: CBS

As already mentioned, due to the strict GMO regulations in the EU compared to other non-EU countries, the application on NPBTs is mainly focused on countries outside of Europe. Activities with these NPBTs within Europe are reduced to a minimum (Sprink et al., 2016). The current process-based legislation, has impact on the competitiveness of the Dutch breeders in the international field already in the short term (Wesseler et al., 2019). A more product-based strategy has the potential to substantially reduce the costs for plant breeding and hence to increase investments in the Netherlands and to strengthen the competitiveness of the sector. Also, an extra quality label could be given to the related products. This benefits the quality of Dutch plant breeders and allows for a responsible introduction of related products to the European market (Rikilt).

Similarly, current global segregation between different regulatory strategies for the market approval of products from new breeding techniques will likely result in an increasing number of import issues. Extra hurdles for the import of raw materials will negatively affect the European economy at large. The extent of these effects will require further investigations (Rikilt).

At the same time current developments in plant breeding may also offer new possibilities for the sector. There seems to be global concern over the potential of the new gene editing technique in food applications (Agapito-Tenfen et al., 2018). If Dutch/European crop plant products can show that European plant breeding companies have breeding programmes with built-in well-established risk assessment strategies this may further add to quality perception of Dutch/European products. As major modifications become more standard, this quality perception is important for the European and Dutch plant breeding sector (Rikilt).

#### A4.2.2 Economic benefits of NPBTs

The introduction of NPBTs has several economic benefits. Cultivating GM crops can reduce the environmental burden caused by the agricultural sector in different ways. First, the impact of the agricultural sector on the environment has been reduced by introducing crops with insect resistance or herbicide tolerance (Kluemper and Qaim, 20??). An example is the introduction of Bt cotton in the US to control the pink bollworm in cotton (Lotz, van de Wiel & Smulders, 2020). The impact of these agro-chemicals can be measured via an universal tool, the Environmental Impact Quotient (EIQ) (Backus et al., 2008; Kleter et al., Wesseler et al., 2014;). The EIQ is often used to compare use of different volumes of active ingredients in relation with the environmental and toxicological impact of these agro-chemicals. This quotient shows annually the environmental impact of the reduction of the total pesticide use and the impact it has when replacing a certain pesticide with another (Bennett et al., 2013). The environmental impact of GM crop use in the period of 1996-2015 is summarized in the paper of Brookes and Barfoot from 2017. They used the EIQ to change in environmental impact when a GM crop is used compared to the use of a conventional counterpart. In Table 2.1 and Table 2.2 the EIQ changes of GM HT soybean and GM HT maize are shown for five different countries.



**Table 2** GM HT soybean: Summary of active ingredient usage and associated EIQ changes 1996-2015

Country	Change in active ingredient use (million kg)	% change in amount of active ingredient used	% change in EIQ indicator
Romania (to 2006 only)	-0.02	-2.1	-10.5
Argentina	+11.3	+1.2	-8.6
Brazil	+33.7	+3.2	-6.4
US	-32.7	-3.2	-23.3
Canada	-2.8	-7.7	-23.6
Paraguay	+4.2	+5.9	-6.1
Uruguay	+0.83	+3.2	-6.8
South Africa	-0.48	-6.8	-21.5
Mexico	-0.02	-0.9	-4.2
Bolivia	+1.3	+5.8	-4.3
<b>Aggregate impact: all countries</b>	<b>+15.3</b>	<b>+0.5</b>	<b>-13.9</b>

Notes: Negative sign = reduction in usage or EIQ improvement. Positive sign = increase in usage or worse EIQ value

**Table 3** GM HT maize: Summary of active ingredient usage and associated EIQ changes 1996-2015

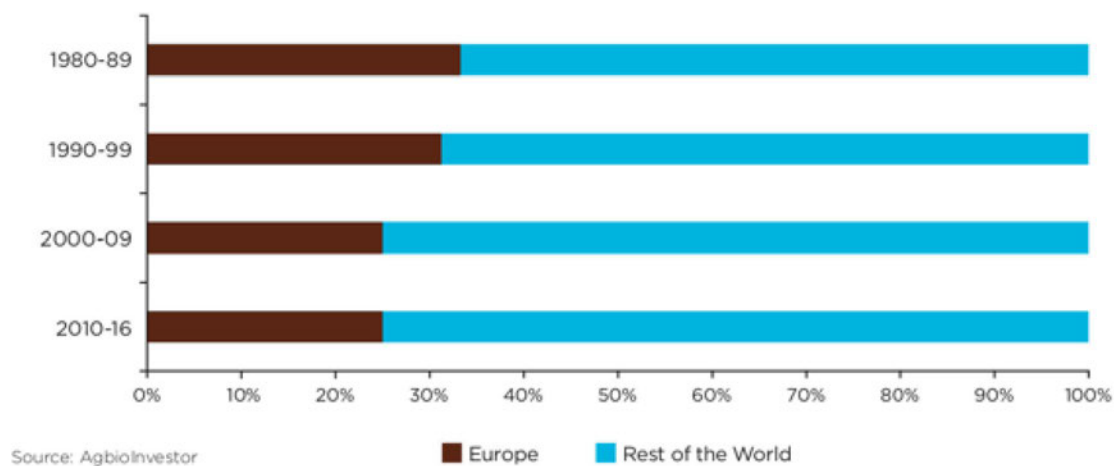
Country	Change in active ingredient use (million kg)	% change in amount of active ingredient used	% change in EIQ indicator
US	-204.4	-9.9	-13.7
Canada	-10.2	-17.3	-20.6
Argentina	-0.6	-0.6	-6.7
South Africa	-2.7	-2.5	-6.8
Brazil	-8.1	-2.6	-8.9
Uruguay	-0.02	-0.2	-9.3
<b>Aggregate impact: all countries</b>	<b>-226.3</b>	<b>-8.4</b>	<b>-12.7</b>

Notes:

1. Negative sign = reduction in usage or EIQ improvement. Positive sign = increase in usage or worse EIQ value

2. Other countries using GM HT maize – Colombia, Paraguay and the Philippines, not included due to lack of data. Also, hand weeding is likely to be an important form of weed control in the Philippines suggesting any reduction in herbicide use with GM HT maize has been limited

Table 2 indicates that the adoption of GM HT soybean in the period between 1996 and 2015 would give a small increase in the active ingredient herbicide used of 0.5%. However, the EIQ indicator shows an improvement of the environmental impact by 13.9% compared to its conventional counterpart, due to the use of environmentally friendly herbicides. In case of GM HT maize (Table 3), the adoption of this GM crop has resulted in a significant reduction in the use of herbicide active ingredients with 8.4%. Also, the environmental impact of the crop has improved compared to its counterpart by 12.7% as indicated by the EIQ (Brookes & Barfoot, 2017).



**Figure 2** Declining share of active ingredients introduced in the EU versus Rest of World

Smyth et al. (2011) report that the introduction of HT canola in Canada reduced the quantity of active ingredient applied by 1.3 million kg over the time period from 1996 to 2007 resulting in a decrease of the cumulative environmental impact by 50% applying the EIQ methodology. A much larger amount than reported by Brookes and Barfoot (2017) for Canada.

The share of active ingredients has not only decreased via the introduction of GM crops. Environmental regulations have also contributed. As can be seen in Figure 2, the share of active ingredients used in the EU compared to the rest of the world has decreased over time. In 1990, the total pesticide use in Europe was 490496 tons and in the rest of the world 1.795.383 tons. In 2017 this pesticide use was 476138 tons in Europe and in the rest of the world 3.637.452 tons (FAO, 2019). In the rest of the world, the pesticide use increased by more than 100% while in Europe it decreases slightly. This indicates that the share of pesticides in the EU compared to the rest of the world declined over the years. This can also be seen in Figure 2 in the share of active ingredients.

For insect resistant GM crops, literature on the pesticide use often indicates the reduction of the use of pesticides on these insect-resistant crops. This reduction of pesticide use improves the associated EIQ value, compared to the conventional counterparts (Kleter et al., 2007; Wesseler et al., 2014).

A second economic and environmental benefit is the reduction of the demand for agricultural land. GM crops that have traits which facilitate crop protection can lead to higher yields as other crop protection measures cannot avoid biotic stresses. If a higher yield could be obtained without an increase in the environmental burden, it could be considered as enhanced sustainability as less land is required for the same production (Backus et al., 2008; Barrows et al., 2014). GM crops can enhance yield by 34%. There is also a direct impact on these NPBT in reducing GHG emissions due to the increase in yield (Bennett et al., 2013). Besides this, GM crops with a tolerance for abiotic stresses such as drought, salt and cold or heat wetter, could be used on land that is not suitable for conventional crops. Therefore, more agricultural land could be available in this case. Another benefit is that GM crops can stimulate the use of agricultural practices that are beneficial to the environment. Herbicide tolerant crops improved the chemical weed control and reduce the dependency on seed-bed preparation and soil cultivation to have an efficient weed control. As a consequence, the herbicide-tolerant crops have eased the implementation of the soil conservation system. This is a reduced tillage system and it has a number of advantages compared to the conventionally ploughed systems. It has an increased carbon storage in the soil, a more diverse soil life, less erosion and a reduced CO<sub>2</sub>-consumptions while ploughing. Meanwhile, these soil conservation systems can cause for a higher pressure of particular diseases, weeds and plagues (Backus et al., 2008). Smyth et al. (2011) calculated that the introduction of herbicide resistant canola in Canada reduced the emission of carbon by one million tonnes annually.

Another environmental and economic benefit could be the reduction of the use of fertilizers. Nitrogen fertilizer is needed as nutrient to grow healthy crops. However, most plants only absorb half of the

nitrogen that is used to fertilize the fields. Researchers are developing GM crops that absorb fertilizers more efficiently. Therefore, farmers have to apply and purchase less fertilizers. This is beneficial for the environment as it reduces the nutrient pollution of the waters. Moreover, it is economic beneficial as fertilizers are a high cost for farmers in the production of crops (see Table 4) (Watson, 2019). The last benefit is the reduction of environmental burden of crop processing. The processing of crops becomes more efficient with less waste and energy use (Graff, Hochman & Zilberman, 2009).

**Table 4** Different receipt costs per hectare in the period 2009-2013

€ per hectare		2009	2010	2011	2012	2013
<b>Receipts per hectare</b>		<b>669</b>	<b>946</b>	<b>1029</b>	<b>1196</b>	<b>1060</b>
Specific costs	Seeds	55	59	64	72	76
	Fertilisers	151	138	158	188	194
	Crop protection	90	103	105	116	123
	Water	0	0	1	1	1
	Other specific costs	12	13	13	14	12
	Total	309	314	340	391	405
<b>Crop protection as % of specific costs</b>		<b>29%</b>	<b>33%</b>	<b>31%</b>	<b>30%</b>	<b>30%</b>
Non-specific costs	Motor fuels	58	72	82	93	91
	Upkeep	49	61	56	58	58
	Contract work	44	56	61	61	64
	Energy	8	10	11	12	11
	Other direct costs	60	73	77	83	84
	Total	220	272	286	306	307
<b>Gross margin</b>		<b>140</b>	<b>360</b>	<b>403</b>	<b>499</b>	<b>348</b>
Other farm costs	Depreciation	122	143	149	157	170
	External factors	149	171	174	189	193
<b>Net margin</b>		<b>-131</b>	<b>46</b>	<b>80</b>	<b>153</b>	<b>-15</b>

Source: EU FADN

#### A4.2.3 Current situation NPBTs in Europe and the economic implications

The most important piece of legislation in the EU with regard to GM food and feed is Directive 2001/18/EC. In the appendix of this paper an overview of the regulatory process for GM plants is given. The directive is amended multiple times and governs the 'deliberate release of GMOs in the environment'. It therefore covers the cultivation and imports of GMOs. Because it is a directive, the EU lays out common goals for its Member States, but the Member States have to achieve these goals and may determine how they will achieve them. Besides this, there are regulations for the authorisation, labelling and the placement on the market of GMOs that are meant as food or feed (Punt & Wesseler, 2015). Regulation EC No 1829/2003 lays down the procedures that have to be taken for the authorisation of genetically modified food and feed. This Regulations also includes the labelling requirements for these food and feed.

An example of the complex and uncertain regulatory approval process of the EU is the insect-resistant maize MON810. This crop was approved in 1998 for commercial cultivation in Europe. However, it would be unlikely that this crop would receive regulatory approval today, even if the product is proved to be safe. This is caused by the regulatory approval process of the EU. The EFSA has a starting position in this approval process in evaluating the crops. Only crops that meet with the strict biosafety criteria of the Commission are put forward. The Commission then has to draft a decision that is submitted to the Member States Expert Committee. To get approval for the cultivation of the crop, a qualified majority voting is required and therefore it needs the support of Member States. In 1998 there were 14 member states, now there are 27 member states. This makes it harder to reach a qualified majority. All products derived from GMOs require a renewal of approval every 10 years. For maize MON810, this renewal is still pending since 2007 as no majority vote has been reached (Hundleby & Harwood, 2019).

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The EU's attitude towards the cultivation of GM crops can also be seen in the research area. The number of field trials in Europe has declined with 90% between 2010 and 2016. This indicates a negative trend in the R&D of the GM technologies in Europe (Hundleby & Harwood, 2019).

The growth of the agricultural sector in the EU has been stagnating in the last decade compared to the main agricultural producers. According to results from DG AGRI and the USDA, the total productivity factor of the EU has decreased since 2002 and has shown a growth of 0.3% in the period 2002-2011. In the US a stronger, increasing growth has been estimated of 3.1% in the period 2006-2010. The Netherlands is one of the best performers when it comes to productivity compared to other EU Member States (Baráth & Fertő, 2016). The political environment in the EU contributes to this stagnating agricultural sector. Policy decisions and regulations have resulted in a lower access to modern agricultural techniques and tools among which plant biotechnology. This approval process has proven to be very politicised. As a result, the process becomes very lengthy, costly and unpredictable. This is mainly caused by the scientifically doubtful objections that are raised by Member States individually (Leopoldina, 2019). This makes the region less attractive for private companies to conduct their research and development for new plant breeding technologies.

## A4.3 Animals

### A4.3.1 Economic importance animal sector

Animal agriculture is a highly important sector for the Dutch economy and economic perspectives.

The livestock sector generates around €9.3 billion per year in the Netherlands (Government of the Netherlands, n.d.). Moreover, animals are also used in the pharmaceutical industry.

New breeding techniques may increase production characteristics of animal-based food products either when beneficial traits are introduced that directly influence yield (faster growth, increased muscle tissue) or through the introduction of traits that stimulate animal health and welfare (disease resistance/tolerance). Both of these strategies can have a potential beneficial economic advantage both for animal breeders and consumers (Rikilt).

When livestock animals grow faster this cuts down on the time needed for the animal to reach a marketable size, and increased muscle tissue directly increases the yield of meat. Both of these examples may also have the added benefit of higher feed conversion efficiency, animals that reach the proper size more quickly may, therefore, need relatively less feed (Rikilt).

Traits that reduce the occurrence of diseases by improving disease resilience may clearly also have economic benefits. Reducing the impact of diseases decreases animal suffering with related adverse effects for the growth characteristics of the animals, will reduce the costs associated with veterinary consultations, treatments and in case of potentially virulent pathogens will prevent the untimely culling of livestock. More efficient and disease-free production of animal products could potentially reduce the consumer price for meat based products (Rikilt).

Cloning and genetic modification of livestock are globally inevitable. Too strict regulation concerning these developments threatens the European progress. Current developments in livestock biotechnology indicate that these programmes are mainly carried out in non-EU countries and therefore, the EU may be losing its competitive advantage (Twine, 2010). Within the EU, certain animal biotechnology projects are being carried out for agricultural purposes such as research on African swine fever resistance at the Roslin Institute in the UK. Commercial application of animal biotechnology in the EU is regulated under the same process-based legislation as for GM plants, with an additional focus on animal welfare aspects. However, no GM animal for food use has been commercialized in the EU, and at the time of this writing no applications have been submitted to EFSA for the placing on the market of GM animals (Rikilt).

Similarly, current global segregation between different regulatory strategies for the market approval of products from new breeding techniques will likely result in an increasing number of import issues. The extra hurdles for the import of raw materials will negatively affect the European economy at large. The extent of these effects will require further investigations (Rikilt).

At the same time current developments in animal breeding may likewise also offer new possibilities for the sector. There seems to be global concern over the potential of the new gene editing techniques in food applications. If Dutch/European animal products can show that European companies have animal breeding programmes with built-in well-established risk assessment strategies and clear animal care standards this further adds to quality perception of Dutch/European products. This may benefit the sector, especially in times to come when major genetic modifications may become more standard (Rikilt).

The aquaculture sector becomes more and more important to food security compared to the fishery sector. Fish is an important food source for humans and source of income for both developed and developing countries. Wild captured fishery practices are threatening the fish stock worldwide. Aquaculture is therefore proposed to increase the sustainable fish production. In 2025, aquaculture should account for more than half of the worldwide fish production. To meet this increasing worldwide demand for fish, new techniques have to be applied (Msangi et al., 2013). Modern biotechnology could be one of the solutions to meet this demand. Fish that are genetically modified could make aquaculture more effective (Haro, 2012). Fish that are produced by using GM technologies could have an increased growth rate, increased tolerance to different temperatures and improvement in disease resistance. So far, only one GM fish breed has been commercialized, the AquAdvantage salmon. This commercialization is only been happening on a limited scale in a single country (Canada). Several other GM animals were already used for medicines and other non-food products, but the AquAdvantage salmon was the first genetically modified animal that was licensed for human food consumption (Kleter, Liang, van der Berg & Kok, 2019).

**Table 5** Projected Total Fish Production by Region

	Data (000 tons)	Projection (000 tons)			Share in global total		% change
	2008	2010	2020	2030	2010 (projection)	2030 (projection)	2010-30
Global total	142285	151129	172035	186.842	100,0%	100,0%	23,6%
ECA	14564	14954	15369	15700	9,9%	8,5%	5,6%

**Table 6** Projected Total Food Fish Consumption by Region

	Data (000 tons)	Projection (000 tons)			Share in global total		% change
	2008	2010	2020	2030	2010 (projection)	2030 (projection)	2010-30
Global total	111697	119480	138124	151771	100,0%	100,0%	27,0%
ECA	16290	15488	15720	16735	13,0%	11,0%	8,1%

**Table 7** Projected Total Fishmeal Production by Region

	Data (000 tons)	Projection (000 tons)			Share in global total		% change
	2008	2010	2020	2030	2010 (projection)	2030 (projection)	2010-30
Global total	5820	7044	7401	7582	100,0%	100,0%	7,6%
ECA	703	1000	1005	1008	14,2%	13,3%	0,7%

**Table 8** Projected Fishmeal Use by Region

	Projection (000 tons)			Share in global total		% change
	2010	2020	2030	2010 (projection)	2030 (projection)	2010-30
Global total	7045	7402	7583	100,0%	100,0%	7,6%
ECA	1009	1075	1195	14,3%	15,8%	18,5%

ECA=Europe and Central Asia; Source: World Bank

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As can be seen in the tables above, the total fish production in Europe and Central Asia will potentially increase by 5.6% in the period between 2010 and 2030 while the fish consumption will increase by 8.1%. This would mean that the growth in supply will increase less than the growth in demand in this region. Compared to the global total this increase in production and consumption is significant lower (growth in world production is 23.6% and consumption 27.0%).

When looking at the fishmeal use in Europa and Central, the increase in the period of 2010-2030 is significantly higher than the rest of the world (18.5% and 7.6% respectively). However, the growth in production of fishmeal in Europe and Central Asia is much lower compared to the rest of the world (0.7% and 7.6% respectively). This shows that Europe has a growing demand in both fish products both for consumption and fishmeal. Due to this growing demand Europe becomes more dependent on new techniques and countries outside Europe to meet the demand (Msangi et al., 2013).

#### A4.3.2 Economic benefits of genetically modified animals

There are already some GM animals being produced for the improvement of livestock production. Examples of these improvements are the increase in quality of the (end) products such as milk or meat, disease resistance and the increase in growth of an animal (Mora et al., 2012). Enviropig™ is an example of an application that would help reduce the impact of farming on the environment by the reduction of phosphorus pollution (Suva, Westhusin, Gaddy & Long, 2019). Also, GM animals can be used for human health and bio-medical applications. In this case, GM livestock are used to produce pharmaceutical proteins from fluids like milk and egg white, animal tissue and organs for the use in human transplants and human antibodies.

Genetically modification of animals has a much slower process than crops and therefore analyses of the costs and benefits of GM crops are already often described while the analysis of genetical modifications in livestock is still little. Different factors are playing a role in slowing down the process of producing GM animals among which human health, environmental, animal welfare, socio-economic and technical factors (Mora et al., 2012).

The improvement of the biotechnology in animal production is expected to give economic benefits for farmers, the processors and consumers. For example, GM fish species are already developed that have a larger growing rate than their conventional counterparts. This faster growing rate will result in lower farming costs because the feeding costs are lower and the fish is faster ready to being sold (Bodnar, 2019). This will also result in economic advantages for consumers as the prices of fish become lower (Menozzi et al., 2012). It could also have advantages for consumers because the food can have additional health benefits, the food is safer produced because it comes from healthier livestock and, as already mentioned, the production process of GM animals might have a lower environmental footprint (Mora et al., 2012). Biotechnology could therefore also enhance the health and welfare of livestock. Transgenic sex selection could result in the breeding of only female chicks, which spare millions of males annually from being culled and also have economic benefits as the yield can double. These biotechniques can also prevent cattle from being dehorned as the gene responsible for the horns can be knocked out. Also, the preventions of diseases is beneficial for both the animal wellbeing, human health and the prevention of high costs due to these diseases (Forabosco, Löhmus, Rydhmer & Sundström, 2013)

As can be noticed from recent developments in GM animals, the development in aquaculture is greater than the development of terrestrial animals. The enhanced growth rate of the fish and the food conversion rates can reduce the costs of the production of the fish (Msangi et al., 2013). However, the GM fish farming still causes serious concerns for the ecology and alterations in the production process might be needed which makes the production of GM fish less economic attractive.

This increase in costs in the production of GM animals also occurs in the terrestrial animal sector. Therefore, a higher profit should be reached to make the investments feasible. This makes the application of products derived from GM animals most feasible in the production of high-value pharmaceutical substances. This market is worth billions of dollars and is therefore at the moment the most promising sector for the application of animal transgenesis. However, there are still only a few

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drugs produced that have reached the market because of the financial insecurity firms have during the production phase (Mora et al., 2012).

#### A4.3.3 Current situation genetically modified animals in Europe and the economic implications

Starting in the '90s, Europe has been experimenting with the development of GM animals. Examples of these innovations are Dolly the sheep, the first animal that was cloned by an institute in Scotland and Herman the bull, who had an extra human gene in its DNA (Mora, 2012). Because of this extra gene, his female offspring would be able to produce the human protein lactoferrin in their milk. This protein could be used to make anti-inflammatory drugs (Pascoe, 1994). Other examples of the development of GM animals at European institutions are fish and chicken with benefits for the food productions and in other areas of application. This shows that Europe had considerable innovations in the genetical modification of animals. However, nowadays most of the activities and developments of GM animal technology are taking place outside of Europe (Menozzie et al., 2012). It is possible that these animals will also find their way into the EU through oversea imports, especially because the EU is one of the world's international trading-blocks when it comes to food commodities (Mora et al., 2012).

In the EU, food safety and environmental risk assessments are main steps before a product derived from GM animals can be placed on the market. For example, EFSA has carried out a review for the criteria of an environmental risk assessment for GM fish that could potentially be marketed in the EU (EFSA, 2013). Also, decisions that are made by one country may affect other countries, therefore the decision-making process should be toned as much as possible within the EU (Le Curieux-Belfond et al., 2009). The regulations that are in force will have a major influence on the investments that will be taken by private companies for biotechnology R&D. For example, pharmaceutical companies were not willing to invest in the GM applications for drugs and other pharmaceutical products until they were certain that it would be accepted by regulatory agencies such as the European Medicines Agency (EMA) (Vázquez-Salat and Houdebine, 2013). Another issue with the investments is the expected increase in costs because of the environmental and food safety regulations that can have an effect on the profitability of R&D by companies. This is due to the extended time that is necessary for a product to be approved and be brought on the market and because of the stricter standards that have to be met (Caswell, Fuglie & Klotz, 2003). Regulations and industry practices that are associated with GM animals and the products derived from them should be transparent to gain consumer acceptance. Reliable identification and strict control of an animal is therefore important (Frewer, Coles, Houdebine & Kleter, 2014). This is already done in many forms within the livestock industry, for example by giving animals an ear tag (Gavin, 2001). Also measures to separate GM and non-GM animals from each other along the supply chain to guarantee their coexistence has influence on the willingness of producers to adopt the technology (Mora et al., 2012). This strict and heavy regulatory environment in the EU may therefore have a stronger impact on the breeding sector, because small and medium companies are more limited by these regulation, than in the pharmaceutical sector, where the market is to a great extent harmonized and therefore able to cope with the administrative regulatory burden (Vázquez-Salat and Houdebine, 2013).

Labelling would also be a solution to help making products derived from GM animals more transparent to consumers. These labelling requirements will cause for extra costs, among other the costs of traceability. Other costs that are caused by regulations should also be considered. These costs that are required to comply with the regulations may reduce the profitability of the technology for companies and therefore may also increase the price for consumers. On the other hand, consumers will benefit from these regulations because they reduce the risk of the new technology. These regulations can therefore also be used to balance the costs and benefits of GM animals. These costs and benefits of the new technology and its regulations should be determined to find out whether the use of GM animals is beneficial, both for companies and consumers (Caswell, Fuglie & Klotz, 2003).

Both the EU and USA have a similar regulatory environment with strict regulations for both the food and pharmaceutical sectors (Mora et al., 2012b). China also has a process-based regulations (Ishii & Araki, 2017; Gao et al., 2018). The developments in GM animals has become of importance in China. On paper the Chinese regulations seem to be very strict concerning these GM animals. However,



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Chinese researchers have already produced several GM animals including cashmere goats that can grow longer hair, miniature pigs that are lacking a growth gene and large beagles that are lacking a muscle-inhibiting gene. This edit could provide for faster dogs (NY Times, 2015). This shows that, although the GM animal regulations in China look strict on paper, they are fast in their development of new GM derived animals.

## A4.4 Micro-organisms

### A4.4.1 Economic importance GMM sector

Micro-organisms have been used since ancient times in the fermentation of food. Food fermentation is still applied in the preparation of many food products. Microbial enzymes are often preferred because they are steadier than the enzymes of plants and animals (Gurung, Ray, Bose & Rai, 2013; Raveendran et al., 2018). They are also preferred over the chemical enzyme because of their environmentally friendly origin, high yield, efficient process control and safety (Gurung et al., 2013). Moreover, they can be produced in a cost-effective manner because they require less space and time. Also, process modification and optimization can be easily achieved (Raveendran et al., 2018). Microbial enzymes have an enormous diversity and are therefore used in many areas. They are applied in many industries including agricultural, food processing industry, chemical industry, pharmaceuticals, textile industry, paper industry, analytical applications, cosmetics, detergent industry and environmental pollution control (e.g. bioremediation and biodegradation) (Liu & Kokare, 2017; Raveendran et al., 2018). For example, the microbial enzyme Glucoamylase is used in beer production, Cellulase is used in animal feed and Peroxidase is used for the development of flavor, color and the nutritional quality of food. Various molecular and biochemical approaches could easily modify the microbial enzymes. For example, hyperproduction of the enzymes could be achieved by the overexpression of their genes. There are still a lot of microbial enzymes that are unexplored and this gives opportunities for a wider industrial application, particularly in the food sector (Raveendran et al., 2018).

The bioeconomy plays a major role in the creation of this circular economy as it encompasses the production of renewable natural resources and converting these resources and the waste streams in value added products, processes and services (EEB, n.d.; amfep, n.d.). In the Bioeconomy Strategy, the European Commission points out the importance of the bioeconomy in a world of scarce resources. It is therefore important to seek new and more sustainable ways of producing and consuming because of these scarce resources, growing population, ecosystem degradation and potential climate change. On the other hand, there is a strong incentive to modernize Europe's industries to strengthen the position in a highly competitive global economy (European Commission, 2018). The use of enzymes and industrial biotechnology supports the development of the bioeconomy (Bilal & Iqbal, 2019). Enzymes can be a renewable source as it can be used for bioenergy, pharmaceuticals and in food and feed (Scarlat, Dallemand, Monforti-Ferrario, Nita, 2015). Enzymes can help to convert biomass, that may be obtained from among other things food waste, into biogas, bioethanol or other biomaterials (amfep, n.d.). Producing bioenergy from enzymes can lead to the decarbonization of energy intensive industries and reduces the dependency on oil and other exhaustible resources (Wyns & Axelson, 2016). As already mentioned, enzymes are often used in the detergent sector. Detergents contain enzymes that break down fats, oils and protein chains and are therefore used for stain removal. By using enzymes in detergents, this will result in the reduction of energy and water use (Al-Ghanayem & Joseph, 2020). Moreover, enzymes can replace the use of other chemicals that have more impact on the environment (amfep, n.d.). In food production, enzymes can increase yield, reduce waste and also save energy (Andler & Goddard, 2018). In feed for animals, enzymes can be used to maximize the conversion ratio of feed which reduces the amount of costly ingredients that is necessary for the production and reduces emissions because a lower amount of feed has to be produced globally due to the higher conversion rate (amfep, n.d.).

*Gene editing technologies will help to manoeuvre into new areas of microbial biotechnology*

The current regulatory requirements and safety assessment of gene edited microbial food/feed products will definitely have an impact on innovation within the EU and could delay the pace of

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commercialization. For the Netherlands is important to maintain its strong position in microbial industrial biotechnology, especially in the food and beverage sector where food enzymes (used for starch processing and in the dairy industry) and fermentation products (beer) are examples of important exported products. Europe is a major player on the global market for industrial enzymes such as food enzymes. NGMTs can speed up microbial strain development for the food/feed industry and thus construction and application of microbial cell factories for improved production of enzymes. The development of NGMTs for strain development not only serves for increasing the overall production but it makes it possible to modify new species of micro-organisms that could synthesize novel enzymes or compounds with a potential use as food/feed enzymes or additives. New gene editing tools also make it possible to engineer the genome of a wide range of species, such as microalgae, that were relatively difficult to modify using more traditional genetic engineering methods. Microalgae are a promising alternative source of protein and high-value nutrients for both humans and animals. Algal species designed with NGMTs may positively affect the position of Europe in the new areas of food biotechnology (Rikilt).

#### *Using waste streams with inactivated GE microbes in our future circular agriculture*

As the EU is moving towards a circular economy, residual biomass waste streams from the biobased industries are a promising feed protein source for livestock. For example, Dried Distillers Grain (DDG) or Dried Distillers Grain with Solubles (DDGS) are by-products from the distillery and the bioethanol industries, resulting from the fermentation process of plant-derived sugars into alcoholic beverages or biofuels by genetically modified yeasts (*S. cerevisiae*). In the US, several biomass waste streams with inactivated genetically modified *S. cerevisiae* (IMSC) strains for the use as livestock feed have undergone a GRAS evaluation by the FDA. Several biomass waste stream IMSC strains are now considered safe to use as livestock feed in the US. These *S. cerevisiae* strains are all modified using traditional genetic modification methods. No livestock feed consisting of GM yeast have been authorized to enter the EU market. If the Netherlands and other EU members will move to a circular economy, different biomass waste streams could be considered for recycling as feed materials, including lignocellulosic waste streams containing inactivated GMMs from the biobased industries. It is expected that the biobased industries worldwide, will eventually move to the NGMTs to modify their strains, as it is faster, cheaper and easier than the traditional methods. As for the EU, there are novel safety, traceability and economic issues (e.g. the lack of detection methods) to consider in this area and with these novel GE tools, the GMM safety assessments for livestock feed have to be adjusted accordingly (Rikilt).

#### A4.4.2 Current situation GMMs in Europe and the economic implications

As already mentioned, GMMs are involved in the production process of many industries. Especially in the food and feed industry, the release and consumption of products derived from GMMs raise questions about the safety for human health and the environment. The European Union has therefore established different legislative instruments to make sure that the products are safe. A scientific risk assessment is requested before a product can be placed on the market. The EFSA Panel has published a guidance for the risk assessment of the GMMs when they will be used in food or feed products. The assessment consists of two parts namely the characterization of the GMM and the possible effects that the modification might have on safety, and the product safety itself. The characteristics of the GMM consist of the parental organism, the donor of the genetic material that is used, the genetic modification itself and the final GMM and its traits. Furthermore, the composition, potential toxicity/allergenicity, nutritional value and impact on the environment of the product are evaluated. The outcome of this assessment then undergoes a scientific opinion to indicate whether or not it raises safety issues. This opinion is then used by different European regulatory authorities to decide if the product should be authorized for commercial use (Aguilera, Gomes & Olaru, 2013).

Microbial biological control agents (MBCA) can be very useful for the control of diseases, weeds or pests in crop plants. They may therefore be used as an alternative for plant protection products that have a chemical composition (Scheepmaker, Hogervorst & Glandorf, 2016). They contain living micro-organisms among which fungi, viruses and bacteria. They are regulated at both EU and Member State level in the European Union. To ensure food safety, these MBCAs undergo an extensive risk assessment. This risk assessment was first determined in Directive 91/14/EEC. The Directive was

revoked by Regulation 1107/2009 to have regulatory circumstances that fit better with the requirements of MBCAs. As a consequence, only 26% of the active substances and Plant Protection Products passed the assessment compared to the situation under Directive 91/41/EEC. Due to regulatory complexity, only a few MBCAs are currently available on the EU market. Compared to the USA, the MBCA registration procedure takes substantially more time with an additional 1.62 years on average. This delay in registration results in costs. This EU process for the approval of MBCAs could be compared to the approval process for GMO techniques. This process gives a delay of 1.93 years compared to the USA. The GMO approval process is mainly delayed due to the Member State majority voting procedure. This is not the case for MBCAs and therefore their registration process could potentially decrease (Frederiks & Wesseler, 2019). In the current EU GMO legislation, a genetically modified MBCA falls under the definition of a GMO. Therefore, an environmental risk assessment needs to be done before a GM MBCA can be placed on the market (Scheepmaker, Hogervorst & Glandorf, 2016).

In the food and feed industry, genetically modified microbial strains are used to produce enzymes, flavorings and additives. Food enzymes are evaluated worldwide by the Joint FAO/WHO Expert Committee on Food Additives on a voluntary basis (Deckers, Deforce, Fraiture & Roosens, 2020). The EU decided to harmonize regulations that are related to commercializing of FE and established two regulations. The regulations settle a common authorization procedure for the FE, food additives and flavoring and harmonized the rules on the use of enzymes in food and required a submission of applications to have these FE, food additives and flavoring authorized. The quality control of the FE preparations that are already commercialized are under the responsibility of the manufactures, both in the EU and the rest of the world (Deckers et al., 2020). It is relatively complex to regulate FE under the EU directive 2001/18/EC and (EC) No. 1829/2003. Whether a food is produced 'from' or 'with' GMOs depends on whether there is still GM material present in the food. If feed or food is produced 'with' GMOs, it is not covered by regulation (EC) No. 1829/2003. In this case, the processing aids do not fall under the scope of the regulation. If a feed or food product is produced 'from' a GMO, it does fall under the regulation and need authorization that is in accordance with regulation (EC) No. 1829/2003 and regulation (EC) No. 1332/2008. To determine this whether or not a FE falls under the regulations, it needs to be decided whether it was used as an ingredient or as a processing aid. In case that it was used as a processing aid, it has to be determined whether or not the material from a GMO is still present in the product. If the FE falls under regulation (EC) No. 1829/2003, zero tolerance to the GM production strain is applied. As no FE dossier has been submitted yet under the regulation, the GMMs are automatically regarded unauthorized as zero tolerance is applied (Deckers, Deforce, Fraiture & Roosens, 2020).

**Table 9** Labeling requirements for GM products

GM product	Example	Labelling requirement
GM plants, seeds, and food	Maize, maize seed, cotton seed, soybean sprouts, tomato	Yes
Food produced from GMOs	Maize flour, soybean oil, rape seed oil	Yes
Food additive/flavouring produced from GMOs	Highly filtered lecithin extracted from GM soybeans	Yes
GM feed	Maize	Yes
Feed produced from a GMO	Corn gluten feed, soybean meal	Yes
Feed additive produced from a GMO	Vitamin B2	Yes
Food from animals fed on GM feed	Eggs, meat, milk	No
Food produced with the help of a GM enzyme	Bakery products produced with the help of amylase	No

Source: Commission of the European Communities (2003a)

As can be seen in the table above, food produces with the help of a GM enzyme do not have a labeling requirement. As already was mentioned, enzymes are used in a large range of sectors. If the European Commission to require labeling for these enzymes, it would have large consequences for different sectors. In Regulation (EC) No 1829/2003, the rules for labelling are stated as shown in the

above figure. The regulation should only apply for food and feed that are produced 'from' a GMO but not if they are produced 'with' a GMO. It should therefore be determined whether there is material present in the food or feed that is derived from GM source material. When a GMM is used as an aid in the processing of food and feed, it should not be considered as falling under the regulations and therefore no GMO labelling is required. But if the GMM is not removed from the food enzyme it does fall under the regulation. It necessary to decide whether a food enzyme is used as an ingredient and has to be labelled in the ingredient list or as a processing aid which does not require labelling (European Commission, 2014).

The uncertainty about GMMs in the regulatory environment of the EU is shown in Table 10. Directive 2009/41/EC about the contained use of GMMs gives only certainty about regulating GMMs when it concerns conventional genetically modified organisms. For genome edited organisms there are probable GMMs involved according to the Directive. This is also the case for traditional mutagenesis breeding but these GMMs are excluded from the scope (Leopoldina, 2019). Due to this uncertainty it is more difficult to regulate these GMMs.

**Table 10** Classification as genetically modified organism (GMO), genetically modified microorganism (GMM) and living modified organism (LMO) according to European and international regulations

	Traditional breeding	Traditional mutagenesis breeding	Conventional genetically modified organisms	Genome edited organisms
Directive 2001/18/EC 'GMO Directive'	non-GMO	GMO, but excluded from scope	GMO	GMO
Regulation (EC) No 1829/2003 'GM food and feed'	non-GMO	non-GMO	GMO	GMO
Regulation (EC) No 1830/2003 'GMO traceability and labelling'	non-GMO	non-GMO	GMO	GMO
Regulation (EC) No 2018/848 'Basic Organic Regulation'	non-GMO	non-GMO	GMO	GMO
Directive 2009/41/EC (contained use of GMM)	non-GMM	Probably GMM, but excluded from scope	GMM	Probably GMM
Regulation (EC) 1946/2003 'transboundary movement of GMOs'	non-GMO	non-GMO	GMO	GMO
Cartagena Protocol on Biosafety	non-LMO	non-LMO	LMO	Without foreign gene probably no LMO; with foreign gene probable an LMO

Source: Leopoldina, 2019

## A4.5 Consequences GMO legislation for international trade

The regulations on GMOs in the EU have large consequences on trade with countries outside Europe but also between countries within Europe. For example, in 2013, Europe had authorized only half of the amount of GM plants compared to its main trading partners. Within Europe there are also large differences. Some countries cultivate GMOs, but others only allow imports. Therefore, the policy making in the EU with regard to GMOs is partly decentralized (Punt & Wesseler, 2016). Moreover, Switzerland is not part of the EU but has its main trading routes running through Europe. It has a moratorium on the commercial cultivation of GM crops and animals. A majority of the population of Switzerland voted in a referendum to prohibit the use of GM plants and animals. This ban was extended till the end of 2021 (GMO-free Europe, 2018). Although there is no official moratorium in the

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EU, countries who export GMO products could argue that the process of approval is delaying the approval. However, the EU argues that these delays are necessary to ensure that the products derived from GMOs are safe given the obligations under the Convention of Biological Diversity (CBD) and the Cartagena Protocol on Biosafety (CPB) (Punt & Wesseler, 2016). One of the regulatory approaches that are taken up by the EU consists of the pre-market authorization of GMOs. These are subject to a risk assessment for the environment and human health. If a GMO passed the authorization regime, they are subject to labelling, monitoring, traceability and liability obligations. Mutagenesis techniques are exempted from the GMO regulation because it simulates natural, spontaneous mutations. However, it was not clear which mutagenesis techniques would fall under the mutagenesis exemption as these techniques are the result of human intervention and would therefore fall under the EU law for GMOs. Moreover, it was not clear whether the mutagenesis exemption would also cover the techniques that were developed after 2001 when the directive came into practice. The CJEU made a judgement concerning the legislation of directed mutagenesis under the current regime. This judgement has implications for international trade as other jurisdictions have different approaches towards directed mutagenesis compared to the EU (Eriksson et al., 2018).

The CJEU's ruling may cause disruption in the EU from a trade perspective. The problem is that, in contrast with transgenic plants which are regulated by Directive 2001/18/EC, mutagenic NPBTs are impossible to trace in the final products and are therefore not distinguishable from products that are resulted from an exempted mutagenesis technique or from a natural mutations. This issue in traceability is caused by lack of a well-established identity preservation system (IPS) (Advocate, 2018). It is difficult to establish such a system and this is also very costly (Backus, 2008). The EU agriculture and food sector has therefore liability risks as they might use imported products that were created with NPBTs (Advocate, 2018). The European Union has a positive labelling system for authorized GM traits and a zero-tolerance regime for unauthorized GM traits in force. The negative labelling is not regulated by the EU but at Member State level. The companies in the EU are liable in this zero-tolerance regime. This regime is very strict and companies might be sued because they have GM traits in their products but this is very difficult to trace. This increases the risk of importing products that might contain GM traits. Together with the slow approval process, this zero-tolerance policy on unapproved GM traits makes it very difficult, or even impossible, to cultivate GM crops in the EU (Boccaletti, Passuello & Soregaroli, 2017). Most of these products have to undergo an authorization procedure and labelling and will fall under strict liability regimes and national regulations. Some countries even require that products have a non-GMO declaration before they can be placed on the market. It is almost not possible for companies to immediately obtain a non-GMO declarations because it is not possible to exclude the use of mutagenic NPBT at some point in the creation of the product (Advocate, 2018).

There have been difficulties with importing genetically modified food and feed products from large exporting countries. This is caused by both the zero tolerance threshold level for presence of GMOs that are not yet approved in the EU and the asynchronous approval of GM plants in the EU. This might become even more problematic in the future as the EU keeps importing raw materials from countries where certain GMOs are already approved or in the development stage, but are not approved for cultivation or in food or feed in the EU. These products that contain non approved GMOs should then be taken from the market, even if they are unintentionally present and at a very low level. However, impurities and the presence of unwanted materials is difficult to avoid in traded commodities. This may cause a slowing down or halt in trades altogether, as traders from countries outside Europe are not willing to take the risk of having traces of non-approved GMOs in their shipments. Examples of incidents have already taken place. Because of this, producers of livestock in the EU might be cut off from high-quality feed that is essential to feed their livestock. The demand for this high-quality feed is much higher than the EU can produce by itself as it mostly consist of soybeans and soybean meal (Backus et al., 2008). Only 10-20% of the imports of feed products could be replaced by substitutes for these soybeans (European Commission, 2007). The livestock production has a total demand for feed protein of around 45 million tonnes of raw protein a year, of which one third consists of soybean. The EU could only be self-sufficient for 5% of its protein source. The majority of this soybean protein is imported from countries that already have implemented new and advanced plant techniques, including GMOs (AgbioInvestor, 2018). Without the import of these high-quality soybean based feed, the livestock producers have to switch to more costly alternatives. This may weaken the



competitiveness of the EU livestock production and the companies involved might lose their market position in the world market to countries outside Europe. This can also cause the reduction of agricultural incomes and employment and the increase in meat prices will affect consumers. Consequently, the EU will import its meat from countries that feed their livestock on feed materials that European livestock producers are not allowed to use (Backus et al., 2008).

When looking at the trade deficit, the EU is not self-sufficient in many food products and is therefore dependent on the imports of different crops and products derived from these crops from countries outside Europe. If you only look at cultivated produce is estimated such as cereals, sugar, coffee and tea, fruit and vegetables and animal feed, Europe has a negative balance of €25 million (see Table 11). Especially the fruit and vegetables and coffee, tea and spices show a deficit. Moreover, the EU has a positive balance for cereals and rapeseed trade, but there are still imports necessary for specific varieties of these crops. For some crops such as coffee, tea and rice, cultivation is not possible in the EU climate. However, for multiple crops where there is a deficit in the trade balance such as sunflower, maize, fruit and vegetables and soybean the EU climate would not be a problem (European Commission, n.d.-c).

**Table 11** *EU Trade in Major Agricultural Commodities 2016*

Commodity	Balance of Trade €m.	Balance of Trade Tons m.	Source of Imports (Share of imports in value)
Wheat	4275	27,69	Canada (38.5%), USA (16.7%), Ukraine (14.5%), Russia (8.9%)
Barley	1088	0,38	Ukraine (71.7%), Serbia (5.7%)
Rapeseed	57	0,23	Russia (55.4%), Ukraine (28.6%), China (7.1%), Canada (3.6%)
Sunflower	-599	-3,14	Ukraine (64.2%), Russia (19.5%), Argentina (11.9%)
Rice	-851	-1,68	India (25.4%), Thailand (18.9%), Cambodia (16.9%), Pakistan (12.7%), Indonesia (5.6%)
Sugar	-919	-5,01	Brazil (10.8%), Mauritius (8.1%), China (5.6%), Serbia (4.8%), Mexico (4.2%)
Maize	-1433	-9,67	Ukraine (52.5%), Russia (10.1%), Brazil (9.9%), Canada (6.9%), USA (6.0%)
Soybean	-6285	-18,22	Argentina (47.1%), Brazil (38.0%), Paraguay (7.1%)
Coffee, Tea and Spices	-10927	-4,49	Brazil (13.0%), Vietnam (8.0%), Colombia (3.5%), India (3.4%), Indonesia (3.3%)
Fruit and Vegetables	-18265	-9,39	Turkey (11.3%), USA (11.0%), Brazil (6.1%), South Africa (6.1%), Morocco (5.5%), China (5.2%), Costa Rica (5.0%)
<b>Total</b>	<b>-33859</b>	<b>-23,3</b>	

Source: European Commission

## A4.6 Conclusion

The process-based legislation that is implemented by the European Union is mainly intended to handle uncertainty and safety issues regarding GMOs. Scientific research from the past years has provided a lot of knowledge about the novel technologies and their potential risk. Genetic alteration occurs all the time in nature and it therefore can take place with both novel GE as well as GM techniques. This potential risk could therefore account for both the novel as genetical modification techniques. According to the Directive 2001/18/EC, the product itself also has to be examined if a particular technique is used that is related to the EU GMO regulations. Therefore, a product-based approach is also used in the legislation. More products would be allowed under a product-based approach as the end-product is assessed instead of the whole process (Sprink et al., 2016). Also, the recent CJEU decision has placed NPBTs under the regulations of GMOs (Wesseler, Politiek & Zilberman, 2019). Multiple non-EU countries are already further in their development of these new techniques in plant, animal and microorganism processing due to their less strict regulatory environment compared to the EU. This has major economic consequences as European countries, among which the Netherlands, might lose their leading position in the world market in the agricultural, livestock and microbial sector.



Due to higher marketing costs, R&D concerning these new techniques moves out of Europe and gives other countries a competitive advantage. This mainly has an effect on smaller/medium sized European companies as they are less able to cope with the increasing costs for R&D or are not able to move part of their production process outside Europe. And even if companies move their research to countries with less strict regulations for GMOs, the export of these products remains an issue.

These novel techniques could also help to establish a circular economy and decrease pollution. Moreover, if certain techniques such as NPBTs do not fall under the GM regulations, the labelling requirements will become more simplified which reduces costs (Wesseler, Politiek & Zilberman, 2019). It is therefore important for the EU to be less strict in their legislation towards GM techniques. This could be achieved by switching to a more product-based approach to assess the end products instead of the whole process that is necessary to derive these products. Products will still be regulated in this case, among other things by the European food law. This can also be noticed for other countries who already implemented a product-based approach and therefore have a less strict regulatory process. However, the success of this product-based approach is depending on how it will be interpreted. If the request for GMO product authorization would be more similar to the already existing novel food authorization, this would reduce time needed for the authorization process. The Commission has the authority to decide to place the products on the European market and if the product might have effect on human health, a risk assessment will be requested by EFSA. The standing Committee has to vote in favor of the product before it can be lawfully placed on the EU market. This process will also hold for products from a third country (European Commission, n.d.-b). Such a regulation will simplify and shorten the authorization process, and therefore make the process clearer for both producers in the EU and from outside the EU that are exporting their products to Europe. This will reduce costs these producers and increase the competitiveness of the European market.

## A4.7 References

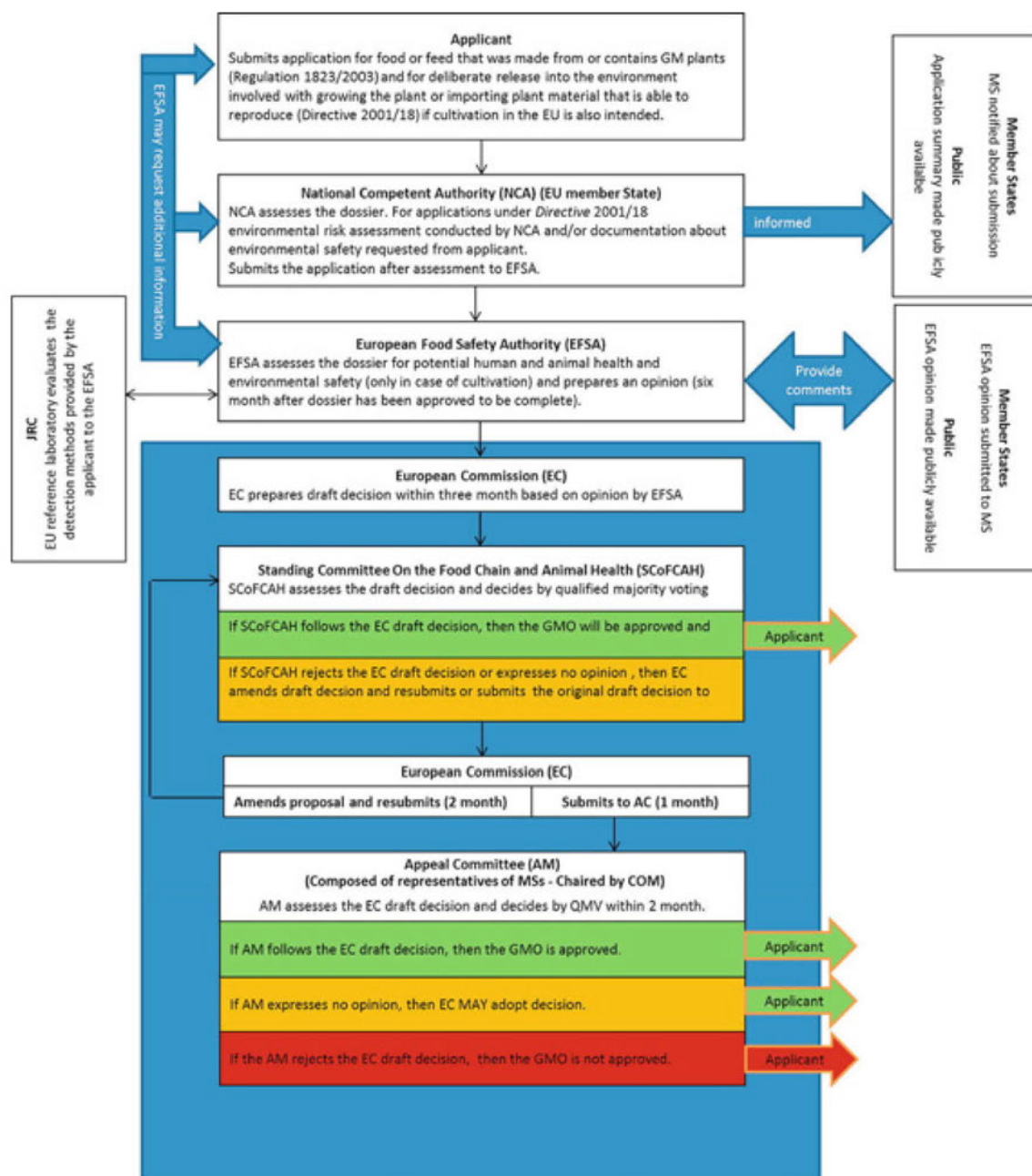
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## A4.8 Appendix



Source: Wesseler & Kalaitzandonakes, 2019.

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