Report of the COGEM International Symposium:

Gene Edited Crops;

Global Perspectives and Regulation

10 October 2019, The Hague, The Netherlands

COMMISSIE COGEM GENETISCHE MODIFICATIE

Gene edited crops; global perspectives and regulation

Although in 2018 the EU Court of Justice ruled that plants obtained by targeted mutagenesis or gene editing are GMOs, and do not fall under the exemption of the EU Directive as they are not derived by classical mutagenesis, gene editing of crops is still a hot topic of debate in EU. Many stakeholders advocate the transition to a product-based legislation to make the GMO legislation future-proof and stimulate innovation. Other parties warn of risks of 'hidden' GMOs, stressing the importance of the precautionary principle or argue that exemption would lead to legal uncertainty for the organic sector and jeopardise freedom of choice and GMO-free production.

During the International Symposium on the 10th of October 2019, organized by the Netherlands Commission on Genetic Modification (COGEM), the possibilities and limitations that gene editing offers for plant breeding and crop improvement are discussed, meanwhile addressing the global perspectives and the worldwide differences in regulation and governance.

More than 100 scientists, policymakers, consultants, regulators and representatives from breeding companies around the world, gathered on the 10th of October 2019 in the beautiful, richly decorated Assembly Hall of the Senate of the Dutch Parliament in The Hague, to discusses the complicated issue of gene editing of crops in light of the ruling of the European Court of Justice and the different global developments. The location was chosen carefully. "The Senate has a special position in the Dutch parliament as it is referred to as the *chamber of reflection*," said professor Sybe Schaap, Chairman of COGEM, during his welcome speech. "It is an appropriate metaphor for the subject of today's meeting since all the discussions on gene editing and its consequences require reflection."

More than 100 participants gathered in the 'Chamber of reflection' to join the discussion on gene edited crops, global perspectives and regulation

Opening speech

Minister Cora van Nieuwenhuizen of the Ministry of Infrastructure and Water Management, who gave the opening speech of the symposium, showed an optimistic view about the innovative power of the agricultural industry in the past and into the future. "Innovations that made plants more resistant to diseases and more tailored to human needs and preferences. Innovations that gave us sweet Brussels sprouts and all

kinds of coloured carrots. Innovations that can help us to grow sufficient food also for the future."

Setting the Scene
The debate about new plant breeding techniques is not new. Following the 2006 policy report on 'New techniques in plant biotechnology', COGEM organised a meeting in 2008 under the admittedly somewhat boisterous title 'The new GMO debate: a clash between legislations'. At that time targeted mutagenesis was still in its infancy. In the recent years the possibilities for making specific changes in genomes have increased enormously. The CRISPR-Cas9 system and upgrades offer previously unheard possibilities for altering genes and the genome, and opens the door to new types of crops and products. Since 2007, politicians and policymakers in the EU have been critically examining various new plant breeding techniques. But despite these efforts, after twelve years the European Commission has still not come to a decision. The EU Court ruling of 2018 and the technological and economic potential of gene editing and new plant breeding techniques have created a new dynamic and a sense of urgency for new EU legislation that takes into account the latest technologies. The symposium 'Gene edited crops; global perspectives and regulation', provided a platform for discussion and the exchange of viewpoints and ideas on how to deal with the current situation.

"But how can consumers and government officials be able to tell the difference between GMO apples and 'natural' apples, if there is such a thing after centuries of conventional breeding? How can we ban non-registered GMOs from the Dutch Market, if we are not able to trace GMOs? One solution is, that instead of regulating the gene modification process, we need to switch to a regulatory system that is more product based." Van Nieuwenhuizen was confident that policy could change things for the better. "Our legislation has to be up to date and future proof and our decision making process efficient and fair. But the current European legislation for genetically modified crops is not ready for the future. Of course we have to comply with European law. That doesn't mean that the Dutch government will sit on its hands. We will make a strong case in Europe for putting GMO legislation back on the agenda," van Nieuwenhuizen said.

In support of that Schaap handed over the first copy of the COGEM policy report to the Minister. The report addresses the implications of introducing a product-based legislation in Europe similar to Canada. "This study reveals the complexity of the issue and concludes that there is not a simple yes or no. That is why we choose the title: No rose without thorns, expressing the complexity in decision making that has to come," Schaap said.

Prof. dr. Sybe Schaap handing over the first copy of the COGEM policy report 'No rose without thorns' to Cora van Nieuwenhuizen, Minister of Infrastructure and Water Management

Session 1: Plant breeding & gene editing

During this session the perspectives of the plant breeding industry and the organic sector on gene editing for plant breeding and innovation were presented and discussed.

Dilemmas in the assessment of gene-edited crops

Professor Nico van Straalen of the VU University Amsterdam, chairman of the agricultural subcommittee of COGEM and chairing the session, introduced the topic of the day by presenting three dilemmas in the assessment of gene edited crops. One of the questions this new technology raises is whether a gene-edited plant is a GMO, if no foreign DNA is introduced and its genome cannot be distinguished from a non-edited plant. Should certain gene-edited plants be exempted from GMO regulation? “For the moment gene editing is considered as a form of genetic modification, which leads to certain points of friction,” Van Straalen indicated.

The first point of friction or dilemma is that a gene edited crop is a GMO in terms of regulation, independent of the phenotype determining the risk. “We determine the risk based on the phenotypic properties such as toxicity to non-target organisms. That has nothing to do with the way that the crop is made. That is a crucial difference.” The second dilemma is that a gene-edited crop is a GMO in terms of EU regulation, but is made according to a method that could exempt it from regulation. “The classical way to introduce mutations, done by X-rays or by mutagenic chemicals (mutagenesis), is exempted from regulation. So you only evaluate the products of that mutagenesis and not mutagenesis as such. According to COGEM, gene editing is a form of directed mutagenesis. However in 2018 the European Court of Justice has not endorsed this view,” Van Straalen said. The third dilemma is that a gene-edited crop is a GMO even when the genome is altered within the species boundaries. “While a genetically modified plant is defined as a plant that has DNA that is introduced in a way that does not occur naturally. So if a gene-edited plant has no foreign DNA it is still a GMO. That is difficult to accept.”

Nico van Straalen, chairman of the agricultural subcommittee of COGEM, opens the first session on Dilemmas in the assessment of gene edited crops

According to Van Straalen the whole sector including regulating authorities are looking for a way to move forward. “This is not a purely regulatory affair, we need to have the public and the consumers involved, in addition to the (organic) plant breeding sector and scientific research. That way forward can only come from innovation, communication, advice and politics combined.”

The definition of gene editing (or genome editing)
Gene editing is modifying the nucleotide sequence at a defined locus in the DNA of an organism by substituting nucleotides for other nucleotides, deleting part of a sequence or inserting new sequences, by using a guide RNA and an engineered endonuclease to introduce a sequence-specific double-strand break, followed by double-strand break repair.

Perspective of the plant breeding industry: potential and limitations of gene editing

Arend Streng is a patent specialist at Rijk Zwaan Breeding BV in the Netherlands, a family-owned company that develops new vegetable varieties and sells the seeds worldwide. It is one of ten large vegetable breeding companies that together share around 80 percent of the market turnover.
“Although the toolbox of plant breeders has been enriched over the years which enable us to breed very efficiently and goal-oriented, developing a new vegetable variety can still take from six to sixteen years of breeding before it is on the market,” Streng said. Now there is gene-editing.

According to Streng, gene editing is very powerful tool added to the toolbox to do genetic research and gain knowledge in order to improve or create new phenotypes, and Rijk Zwaan uses it as such.

Gene editing also offers possibilities to develop and create varieties more efficiently. It could dramatically reduce the time and need for backcrossing processes to get rid of unwanted mutations, as is the case with conventional mutagenesis. But at the moment that is a step too far because of all kinds of technical complexities. “We still know very little with respect to which genes and which mutations will have a positive effect on traits in the crops. For every crop effective gene editing methods have to be developed, and how to grow plants from the edited cells.” For all these reasons conventional mutagenesis for vegetable seed breeding is still an acceptable alternative.

Arend Streng, patent specialist at Rijk Zwaan Breeding BV

For plant breeding companies operating worldwide, the legal framework is also very important. In Europe the legislation is clear, but outside products of gene editing can in some countries be treated as GMO and in others they are not regulated. “The vegetable breeding companies have therefor decided not to introduce GMOs on the market and not to use genetic modifying technology in the development of new varieties.” This decision includes also aspects of liability risks, high cost for licenses and a negative image of genetically modified food in general.

“So if you want to start a range of gene edited varieties for different regulatory frameworks in different countries, it means that you have set to set up a parallel company for the gene edited varieties range. Needless to say that all of these developments would lead to high costs and an unequal worldwide playing field.”

The position of the organic agriculture on gene editing

There is a consensus about the position of the organic sector on the issue. The worldwide standards of organic agriculture do not allow genetic engineering or any products derived from genetic engineering, explained Edith Lammerts van Bueren, professor Organic Plant Breeding at Wageningen University & Research and Louis Bolk Institute in the Netherlands. Gene editing techniques are not compatible with the organic norms and values.

Edith Lammerts van Bueren, professor Organic Plant Breeding at Wageningen University & Research and Louis Bolk

During her talk she provided the context of this position of the organic sector on novel breeding techniques. The major concerns are about environmental and health risks, the socio-economic and legal consequences, and respect for the values of organic agriculture. The latter being the strongest argument. The federation IFOAM has formulated the values of organic agriculture in four basic principles, the principle of health, of ecology, of fairness and of care. Those values have led to the organic rules and regulations which are solidified values. “When proponents of biotech ask the organic sector why they cannot change or relax their rules and use these wonderful tools to solve the world food problem, they ask in fact to change the underlying values,” Lammerts van Bueren explained. “Another aspect to consider is that the organic certification is based on the agricultural process and is not product based. So breeding techniques are not neutral tools and thus evaluated for compliance with the norms and values of this sector.”

Furthermore it is good to realize that it is key to the organic sector to work within the boundaries of living organic nature with respect for the integrity of life and the integrated whole. Techniques that interfere directly at DNA level violate the integrity of life as part of the principle of health, and do not comply. The organic agriculture contributes to

pluriformity in agriculture and society, concluded Lammerts van Bueren. “To improve organic farming systems, there is sufficient scope for innovation within classical breeding. And the bridge to modern genetic knowledge is the use of molecular markers when appropriate.”

The ambition for the future of the organic sector, as stated in the IFOAMs future vision Organic 3.0 for 2030, is to strive for 10 percent organic agriculture worldwide. “We don't only want to grow, but we also want to develop more sustainability. There are more ways to solve the world agriculture food problem.”

Discussion Session 1

Responding to the call of Nico van Straalen **to include the public and consumer** for further development, Edith Lammerts van Bueren hoped that it was not meant to convince them to accept new techniques, but to explore different approaches and keep that window open for the diversity. Van Straalen confirmed that: “Public participation is very important and may become in the present society even more complicated. The European Union has the instrument of civilians initiatives, but it is not really effective. For real public involvement we need more effective instruments so we gain the trust of the public. I think that is one of the most crucial aspects in the whole GMO debate.”

Although gene editing is a step too far for vegetable breeders like Rijk Zwaan at the moment, a member of the audience wondered how they will **tackle particular challenges** for example **in relation to climate change** where gene editing is really needed to obtain certain traits, for example resistance against drought, a multigene genetic kind of trait. Arend Streng confirmed that there are indeed certain traits which can only be solved efficiently with gene editing and not by the conventional mutagenesis, for example a disease resistance in a crop like spinach. “But as mentioned our current technology is still very limited.” The organic breeding sector is also affected by climate change and searches for approaches to respond to that. “One of the approaches is to create more buffer capacity within the so-called variety concept, to overcome different and more unpredictable weather patterns,” added Edith Lammerts van Bueren.

Another member of the audience thought it was **a missed opportunity** that the organic sector especially in the field of disease resistance is disregarding gene editing. “Also in organic agriculture there are a lot of organic pesticides being used that would be good to get rid of. By gene editing the end product cannot even be seen as being different from traditional breeds varieties. So what is the problem?” Edith Lammerts van Bueren explained that this point of view ignores the fact that organic agriculture is certified based on the process and breeding is part of that process. “We do need disease resistance, but the way to come to such a resistance can be very different and we rather choose for alternative approaches than gene editing solutions.”

Another question from the audience for Edith Lammerts van Bueren was what her **advice** would be **for policymakers**: “do they have to reject gene editing or can they allow these techniques if the conventional sector wants to them, but under safety restrictions?” According to Lammert van Bueren the organic sector does not want to throw a verdict about techniques, but asks for a free space to allow to refrain from it. That requires traceability and transparency about the process. “So I'm a little worried if the rules are going to shift towards a product based evaluation. That would require that breeders give transparency about the breeding process so it can be labelled or traced to give farmers a free choice. This is important for the breeders that breed for the organic sector. The earlier problem that the organic sector had with cytoplasmic male sterility based on protoplast fusion, has been respected by companies like Rijk Zwaan that up till now

separated their breeding lines." So if it already works, concluded the questioner, it does not need regulations. Lammerts van Bueren: "It works because it is based on collaboration and trust and being transparent to each other."

Short Communication

COGEM policy report 'No rose without thorns'

Ruth Mampuys, Scientific Secretary of the Subcommittee on Ethics & Societal Aspects of COGEM, presented the main conclusions of the COGEM policy report "No rose without thorns" that was handed over this morning to the Dutch Minister of Infrastructure and Water Management. The report discusses the possible implications of switching from a process-based regulation to a product-based regulatory system for GM crops in Europe. Canada, which uses this system, has been taken as an example. "COGEM wrote the policy report not to provide the final answer on what system is best, but to stimulate and inform the discussion on this topic," stipulated Mampuys.

The Canadian product based regulatory framework makes no distinction in techniques by which a crop is made. Therefor the system needs no adaptations to new scientific developments or techniques. "However also in Canada there is discussion ongoing about the definition and criteria of new traits, which creates legal uncertainty for developers. There is a low grade of transparency of GMOs in the food production chain, there is no central registration system and there are different voluntarily labelling systems in place," highlighted Mampuys some important differences. The EU regulations on the other hand have a higher level of legal certainty because basically all GMOs are regulated. There is also a high degree of transparency with central registration and detection, mandatory traceability and labelling. The new techniques challenge the regulation due to the decreasing detection possibilities.

"Switching to a product based system, would mean that crops without new traits would not be regulated. It could stimulate the use of new techniques in the plant breeding sector. But it could also aggravate the problem of admixture for the organic sector. It also means that every crop that has new traits will be regulated, including conventional crops. In the Netherlands alone there are about a thousand new varieties registered each year," Mampuys summarized. "Also coordination with other regulations is needed. That some crops will be no longer regulated could have consequences: no central registration of GM crops and no mandatory detection method. This could mean a shift from the administrative burden from the conventional sector to the organic sector. The decreasing possibilities and increasing cost for detection of NPBTs will not necessarily change the procedures and timeline for risk assessment."

The report concludes that the process-based and product-based approaches to regulating GMOs are not simply interchangeable. Both systems have their advantages, problems and disadvantages. "There are differences but the practical differences are sometimes smaller than we think, if you look at the number of crops and type of crops that are regulated in both countries," Mampuys said.

After each session, members of the audience were given the opportunity to exchange thoughts with the speakers

Session 2: Global perspectives on gene editing in crops

Although the situation in the EU has attracted much attention, governments in other countries of the world are also struggling to determine how to regulate gene editing in plants and their resulting products. There are already several countries that have implemented explicit regulatory amendments or interpretations for new breeding techniques, such as Japan, USA and Argentina. Their approaches are presented during this session.

Japan: the latest state of play on genome-editing

"The Government of Japan has always been keen on promoting biotechnology, although consumers do not appreciate the application of this technology in food and say they avoid it," explained Makiko Matsuo, project assistant Professor at the Graduate School of Public Policy, of the University of Tokyo. Japan has a mandatory GM specific framework and safety assessment process for the environment and for food, and labelling is mandatory for GM Food. Because of the low acceptance, there is no commercial cultivation of GM crops in Japan itself. "What the public does not know is that they consume a huge amount of imported GM crops. These crops are mostly used for products that are exempted from labelling requirements, such as oil, soy source and animal feeding."

Genome editing might change all that. Therefore the Government of Japan released this summer their *Biotechnology Strategy 2019* which stresses smart breeding and the operationalization of regulation for gene edited products by 2020. The enthusiastic use of genome-editing in many national research programs has already led to a variety of gene-edited crops and some of them are close to market. Matsuo showed examples from tomatoes with enhanced nutrients, potatoes containing less toxic compounds, high-yielding rice and double muscled fish. Even venture companies arise.

Makiko Matsuo, assistant Professor at the Graduate School of Public Policy, of the University of Tokyo

Efforts to clarify the regulatory status of gene edited products started in 2018. The Ministry of Environment considers the handling of gene edited products under the Cartagena Protocol and looks at the process and the product. If there are no remnants or inserted nucleic acids in the crop or its replicated product than it is exempted from regulation. Otherwise it is treated the same as GM crops. “But even for those products that are out of the regulation, they ask a long list of information about taxonomy, genome editing method, modified gene and its functions, usage of the organism and possible influences on biological diversity and so on. And part of the information provided will be made public on the Japan Biosafety Clearing House (J-BCH) website.”

For food there is a slightly different scheme. The Ministry of Health looks differently at SDN1, 2 and 3 (**see box**). SDN1 is more similar to the conventional breeding and SDN3 is more similar to the GMO regulation. SDN2 depends on the final product and it is up to the Ministry of Health to decide in which category it falls. Therefor a prior consultation process is in place. If the product falls under GM regulation then the mandatory safety assessment is required. However products that are not considered GMO have to follow the notification process.

Also the legislation for labelling of genome edited food products placed on the market (announced 19th Sep 2019) is clarified. “GE products under the GM food legislation have mandatory labelling. Products not considered GM food do not require labelling, however

The three main applications of gene editing in plant breeding:

- SDN1: deletion of unwanted traits. It is replacing the extensive use of mutagenesis to obtain desired traits.
- SDN2: substitution of one gene version (allele) for another. It is seen as a replacement of the backcrossing procedure that is widely used in breeding.
- SDN3: insertion of genes from other species. In the case of sexually compatible species, it replaces the interspecific gene transfer used by breeders over the past century.

(*SDN: Site Directed Nuclease*)

Japan encourages the developers to provide information to the consumers so they can choose."

USA: Gene editing in the USA, a developing perspective

Wayne Parrott of the Institute of Plant Breeding Genetics and Genomics of the University of Georgia, USA, devoted his scientific career to plant improvement. Now two third of the research efforts go to genome editing. "With genome editing (SDN 1-3) plant breeding can be done much more easily and more efficiently. SDN1 technology is now widely used, while SDN2 and SDN3 are still under development. The reasonably permissive regulatory approach for most applications of gene editing has accelerated the use of these technologies, but policy in the US is still evolving. Meanwhile the first gene edited product, Calyxt oil, is already on the market. Other crops are in the pipeline, the acrylamide-free potato, gluten-reduced wheat, SU herbicide-tolerant canola, HT rice and blight-resistant potato," said Parrott. "Now that we are sequencing genomes, we know that the genes that breeders select and cross out are located at the ends of the plant chromosomes. But the genes in the middle, that is about 30 percent of the genes, are not accessible to breeders. With gene editing we are now able to change genes we have never had access to before."

According to Parrot, the Food and Drug Administration, one of the three agencies regulating gene editing in the US, has the most clear approach. "They are still writing their guidance, but what is expected is that they don't care how the seed was made, as long as all food is safe. If plant breeders have any doubt about the safety, they need to consult with the FDA. So far the FDA has not required any editing to be consulted, but the market is asking for it."
The Environmental Protection Agency had not announced its proposed regulation yet. "It is expected that the EPA will only regulate editing if the end result contains pest or disease resistance. EPA is going to release their proposed regulations before the end of this year."

Wayne Parrott, Institute of Plant Breeding Genetics and Genomics of the University of Georgia, USA

The third agency, the US Department of Agriculture, is the most advanced with its proposed regulation. "It has the most ifs, ands or buts of all. If it is a deletion (SDN1) it is not regulated in null segregants (no transgenic modifications in the final product), you don't even have to consult. If it is an allele substitution (SDN2) it is regulated if you use it for agronomical traits. Base editing is not very popular. That is regulated if you change more than one base pair. Insertions (SDN3) are considered transgenes when it comes

from a non-related species or agro is used." The announced regulatory reform of the USDA has been open for public comment and the final rules are going to be announced early next year. "We don't know what they are going to change. Based on the proposed rules, for substitutions the agro part will be going away and substitutions are not regulated if they are from the natural gene pool. Insertions are still transgenes if coming from non-related species, but only the first event of the new gene might be regulated."

Argentina: Experience in Genome Editing Regulation, the preliminary statistics

Argentina was one of the first countries in Latin America to implement a system to evaluate the biosafety of GMOs for agriculture use. CONABIA, the National Advisory Commission on Agricultural Biotechnology, is instrumental in this forerunner position. "In 2014, CONABIA was recognized by the FAO as a worldwide GMO Biosafety Reference Center," stated Agustina Whelan, head of the GMO biosafety team of the Ministry of Agriculture, Livestock and Fisheries in Argentina. "We saw the interest in the new breeding technologies (NBT) in national and international level rising. So we pioneered in the creation of a specific regulation for the use of genetically edited products."

In 2013 CONABIA started to work on NBTs regulation and decided to work with the definitions of GMO and biotechnology as described in the Cartagena Protocol to determine if a Living Modified Organism (LMO) is a GMO or not. This was included in Resolution 701/11 that regulates activities with GMOs for agricultural use.

After two years of debate, Resolution 173/15 was adopted presenting a procedure to determine if a product obtained using NBTs would fall under the GM regulation or not. "The four most important features from this guideline are that the analysis is based on a case by case logic and the resolution is not restricted to a list of NBTs," Whelan highlighted. "If the product is still in the design stage, the developer can consult the committee about the status of the hypothetical product. The biosafety commission must perform in any case assessment in 60 days." Products obtained through any NBT must be submitted to a prior consultation, for which Argentina published the guideline (Res. 36/2019) this year. It states that if the final product does not contain a new combination of genetic material generated by NBTs, the product is not considered a GMO.

"The cases presented so far allowed us to obtain preliminary statistics related to the socio-economic impact of the gene edited products for agroindustry use," Whelan explained. "When comparing the regulatory trajectory of GM products with the gene edited products, we see the innovation speed for GM crops to remain stable, while the new breeding techniques are flourishing very fast. If we look at the total quantity of products, we see that NBTs also provide a lot of opportunities for small companies and

Agustina Whelan, head of the GMO biosafety team of the Ministry of Agriculture, Livestock and Fisheries in Argentina

public institutions to reach the market with gene edited products compared with the multinationals. In case of GM crop approvals it is the opposite."

According to the analysis, it can be assumed that gene editing will be used commercially in a wider variety of species compared with GMOs which are mainly cereals and oilseeds and fibre crops. This allows the arrival of gene-edited crops to a wider universe of agro-industrial producers and chains.

Discussion Session 2

Despite the differences between the regulatory approaches of Argentina, Japan and the US, a member of the audience saw also commonalities. "One commonality is that the process might be a trigger for regulation, but in the end, it is the final product and its genetic makeup that is decisive if a product is regulated by GM regulations or not. **The dividing line** is if the product is similar or indistinguishable to conventional breeding processes or similar to classical GM products." Agustina Whelan indicated that indeed the focus is on the combination of genetic material in the final product, if the product has a new combination of genetic material it is considered GMO. If not, for example in case of a deletion, the final product is not GMO. And if the final product is free of transgenes that might be used temporarily in the process, than the product is considered non GM.

The way Argentina regulates gene editing is a beautiful example, responded a participant of the symposium. It showed that gene editing is actually **a democratic tool**, because a lot of small enterprises and investors have the opportunity to use gene editing for the benefit of society, instead of multinationals. "It helps to make the society more resilient."

Chair Hedwig te Molder and speakers Agustina Whelan, Wayne Parrot, and Makiko Matsuo during a discussion on international policy

Another member of the audience wondered if there are any efforts of **harmonizing the situation in the US** where different agencies regulate different parts of the GM crops. Even within the FDA there are different approaches for plants and animals. Wayne Parrott explained that nobody in the United States wrote any new laws to regulate biotechnology. "So plants ended up in one section for food safety and animals fell into the section of medicine. Both sections had a very different views on the topic and both had to use the existing laws to get the legal authority to do the regulations. That might change, but in the meantime companies move to Argentina were they can work on animals."

Sigrid Bratlie of the Norwegian Biotechnology Advisory Board, wondered if the regulatory systems that are now in place Argentina, Japan and the US, **align with international policy and if they affect international trade.** Agustina Whelan replied that it is first of all important to have a regulation for it, and to collaborate with other American countries,

such as Colombia and Brazil, who have the same perspective as Argentina. Makiko Matsuo thought that in Japan it will become more complex and diverse with the new regulations. “The devil is in the details. For example, I looked into the Australian regulation that looks similar to the Japanese regulation in case of SDN1 for the environment. However they do not have a notification process. That difference could make things complicated. The details could also affect the trade.”

Hedwig te Molder, member of COGEM and professor Science and Technology Communication at Wageningen University, chairing the session, wondered what role the representatives saw for **public debate and dialogue** in influencing the regulatory framework or governance. Wayne Parrott was convinced that the dialogue with scientists has had a huge impact on the way USDA and FDA are thinking about regulation. “However, the public debate has resulted into echo chambers where the believers talk to believers and the non-believers talk to non-believers, but not with each other. On the other hand, the availability of products that benefit the consumer directly like the apples and potatoes has made a huge difference. Recently the ‘impossible burger’ came on the market and it is the fastest selling product in the United States that it is labelled as a GMO. Nobody cares, even people that say to avoid it.”

In Japan, public engagement is now very important and efforts are made to raise public awareness. Makiko Matsuo: “However, departments are struggling how to engage the public. First they try to give the basic information in the hope to solve the tensions. But we need also to communicate, in order to build trust between those who promote this technology and those who are hesitant. The government now also wants the developers and researcher to have more Ethical, Legal and Social Aspects (ELSI) awareness to make them aware of people's feelings.”

Short Communication

Detection of product obtained by new mutagenesis techniques

On 26 March 2019 the European Network of GMO Laboratories (ENGL), representing all European member states, and coordinated by the Joint Research Centre of the European Commission, published a report on ‘Detection of food and feed plant products obtained by new mutagenesis techniques’. Esther Kok, Head of Department of Novel Foods and Agrichains at Wageningen Food Safety Research, that houses the Dutch national reference lab, presented the main conclusions of the report that was extensively discussed within ENGL over a year. “The key question was: can we detect gene edited food and feed, and how?” said Kok. At the moment the approval procedure for a new GMO in the European Union requires a dossier consisting for a large part of safety data and a detection method that specifically identifies the GMO. “In practice what the applicant needs to provide is an event specific method that actually identifies the sequence that bridges the endogenous plant DNA and the genetic construct. If the method is approved and validated it can be used for law enforcement of the GMO legislation,” Kok explained. “In the new situation, in which a gene edited GMO can be a single nucleotide polymorphism or different modifications at different locations in the genome, what is in that case an event-specific method?”

Kok highlighted two important aspects of the report: the market authorization and market control. One of the main discussions around market authorization is about the validation of methods. “Although it is basically possible to detect a specific DNA alteration, it will in practice not be feasible to distinguish if a single nucleotide variation or a small insertion or deletion has been produced by genome editing, by classical breeding or by

natural variation," Kok said. "And even if methods to identify sequences that are related to a certain events are developed, in practice it will not be possible to reach the same level of specificity and sensitivity. That is a very important point because the event specific method is directly linked to the safety dossier." And another issue that hasn't been solved yet is how to deal with multiple DNA alterations in one locus or different loci.

In terms of market control, the annual screenings on commonly used elements that cover most of the known GMOs will not be possible. In practice there are no common elements and new screening methods are needed. "It will be far more difficult to actually detect and identify unknown or unauthorized genome edited products. In practice we will not be able to identify these substances at the border and it may enter European markets unaffected."

Esther Kok, Head of Department of Novel Foods and Agrichains at Wageningen Food Safety Research

Session 3: Normative criteria in regulation

The way to steer development in a society is not something that is only based on scientific perspective. Normative criteria play a the role too. In this session the normative criteria for regulation were discussed.

Is a restrictive policy on GMO morally justified?

A restrictive policy imposes various limitations on the use of GMO, such as through pre-release authorization requirement, mandatory labelling, and de facto bans. "Individual EU member states can opt-out even if the EU commission authorizes a certain crop. That is also why there are hardly any GM crops on the market in Europe," said Klemens Kappel, professor of philosophy at the University of Copenhagen in Denmark. During his presentation he discussed six main considerations in favour of a restrictive policy on GMO crops: risk for health and environment, the precautionary principle, naturalness, socio-economic consequences, consumers' right to choose and democratic legitimacy. These considerations represent a rather sceptical attitude towards the GM crops, according to Kappel. Each of the considerations was followed by arguments as to why they did not support or justify such a restrictive policy.

In case of risks for health and environment people often invoke what is known as the precautionary principle. “This is a complicated discussion among philosophers. But the seriously adverse outcomes in play seem mere theoretical possibilities, we don’t know that these outcomes are even remotely likely,” Kappel said. “But if you want to evoke the precautionary principle to ban GM crops because of this mere theoretical possibility, then you have to think also about the mere theoretical possibilities of not banning the GM crops, for example to avoid a world of famine.”

The issue of naturalness or rather unnaturalness probably concerns the citizens of Europe the most when they worry about the GM crop. Although there are many different conceptions of unnaturalness, in general it can be said that a GM crop is more unnatural than their non-GM counterparts. The more fundamental problem is, what is the moral relevance of naturalness? Is something morally bad if it is unnatural? The short answer was no, but unnaturalness may be a proxy for safety concerns.

According to Kappel none of the above attempted justifications for a restrictive policy are compelling from a philosophical perspective. Even concerns for democratic legitimacy could not justify a restrictive policy. “There are many plausible views on that, and people converge on the view that democratically legitimate policies should reflect the citizens preferences. Provided that these preferences are sufficiently rational and informed,” said Kappel. “And that is a huge issue, because when concerns about risk or unnaturalness are unsupported by empirical evidence or impossible to rationalize, policies should not reflect such a view.”

Klemens Kappel, professor of philosophy at the University of Copenhagen in Denmark

Social, economic and legal factors that affect the regulatory framework for new plant varieties derived from genome editing

With the advent of new breeding techniques, such as genome editing, new challenges are arising for legislators around the world. “There are two distinct reasons for a regulatory update on GM crops: the specific characteristics of genome editing that do not fit into the existing categories of GMO or non-GMO, and the uncertain or inadequate regulatory status quo in many countries,” explained David Hamburger, researcher at the faculty of law of University of Passau in Germany.

The good thing is that there is now legal certainty thanks to the ruling of the European Court of Justice: all genome edited plants are regulated like GMOs. “But that seems inadequate.” There are already several countries that have implemented explicit regulatory amendments or interpretations for new breeding techniques, but still many

countries have to determine how to regulate genome edited crops. “When making a draft of such an amendment regarding genome edited plants and products, the legislator has to take a list of different normative criteria and regulatory factors into account.” Hamburger discussed extensively during his talk the interest of industry, organic and non-organic farmers, consumers rights and interests, the public opinion in general, human health and food safety considerations, food security and environmental protection issues. Interests and factors that are quite diverse and sometimes conflicting.

Extremely important in drafting legislation in a democracy is public opinion. “A nuanced opinion on genome editing is not to be expected. It will be just an extrapolation of negative and positive views on classical genetic engineering which will find its continuation with regard to genome editing in the European Union,“ predicts Hamburger.

Finally the regulatory outcome of these social, economic and legal factors should be legal under the existing legal system of a country. Therefor two main principles are important, the regulation needs to be proportionate and it needs to be coherent with the overall regulatory framework.

“So the regulation must be suitable to achieve that objective and it must not be more restrictive than necessary. But any measure addressing a non-existing or a mere hypothetical risk is unsuitable, because you cannot not regulate hypothetical risks. Also it unlikely that it is necessary for a regulatory regime to regulate mutagenesis via SDN-1/2 as strict as gene insertion via SDN-3. So it is likely that a regulatory regime should differentiate between the different methods of application to be conform with the proportionality test. Also different regulation of conventional mutagenesis and genome editing actually seems to be incoherent. So it is difficult to establish a scientific basis for a stricter treatment of genome edited varieties compared to varieties derived from traditional mutagenesis techniques.”

“The interests at play differ from country to country depending on the respective political, economic, and social circumstances. Therefore the individual country-specific regulatory outcomes regarding genome edited plants are likely to be as manifold as the interests at hand. The respective legislator has the task of identifying these normative criteria and must find a suitable balance between them,” Hamburger concluded.

David Hamburger, researcher at the faculty of law of University of Passau in Germany

Discussion Session 3

A member of the audience was intrigued by Klemens Kappels’ **concept of naturalness**. She wondered if what people consider to be natural or unnatural is open to change, or is it something so intrinsic that it is not possible to change at all. It is known, for instance, that just explaining facts doesn't change how people think about a subject. From his own

experience Kappel could say that people's attitudes about what they say is unnatural are not so robust and can actually change. "In the middle eighties a huge public debate in Denmark concerned IVF fertilization and one of the main arguments against IVF was that it was an unnatural way of conceiving babies. If you ask people now, it is not controversial anymore." The questioner added: "We noticed in studies, that when someone has to ingest something that might be unnatural, they have a bigger fear. But when it comes to medicine or saving a relative, than it is a totally different story."

Another question from the audience for Kappel was if he was in favour of more **stringent regulations of market competition**, since he argued away most of the arguments in favour of regulating gene editing. Kappel replied that he was in favour of all the regulation needed in order to have a well-functioning market, not specifically in more regulation. "What I am worried about is regulation that is based on very bad reasoning and which at the same time is possibly harmful to us." David Hamburger added that it is important to keep worldwide scale and trade barriers in mind. "Especially the WTO law because the legislation of the European Union has to comply with international law obligations as well and not create more trade barriers then already exists. The question is if the current regulatory regime is coherent and proportionate."

Furthermore **the mandatory labelling of GM food products** was questioned, since the product is not identifiable by specific characteristics or physical properties resulting from the GM (e.g. sugar from a GM sugar beet). David Hamburger remarked: "Since it is mandatory, you just have to do it. It is based on a ruling of the European Court of Justice, so in the end you have to follow the court even if you do not agree with that decision."

Another concern raised was to lose governance and probably confidence, now it is almost impossible to detect whether a crop has been genetically modified. "But there are other ways to detect **or trace the course of history of a giving product**. For example, by looking at the chemical properties of champagne, you cannot say whether that bottle actually comes from the Champagne region in France. But you can trace the history of the product. So a possibility would be to implement a trust system as is the case with organic food," suggested David Hamburger. However, another member of the audience doubted if this comparison worked out. "Labelling champagne will bring you a lot of money, but if you label your GM products you create a lot of problems for yourself on the market."

Session Chair Frans Brom, The Netherlands scientific council for government policy, WRR

Short Communication

Public perception of plant breeding techniques

Huib de Vriend of Lis Consult reported on the public survey requested by COGEM last year to gain insight into how citizens perceive genetic modification in relation to plant breeding applications. The study contained qualitative explorations with different focus groups and a quantitative public survey under more than 1000 people in the Netherlands. Realistic examples of applications in plant breeding by conventional breeding, gene editing, mutagenesis, cisgenesis, and transgenesis were used to explore associations with genetic modification. The results were analysed based on personal, technical and societal factors that may affect those associations.

"The focus groups showed that genetic modification is a tough issue. Discussion is hampered by lack of knowledge about these techniques and the applications," De Vriend said. He also found that genetic modification is primarily associated with medical applications. "The survey showed that context is key. People tend to talk about applications, needs and benefits rather than the techniques as such."

Huib de Vriend, consultant and researcher at Lis Consult, The Netherlands

When asked about the difference between the five techniques, the participants made a clear distinction between conventional breeding and the other techniques. "This differentiation seem primarily driven by perceptions of 'naturalness' and 'principles'. They regard conventional breeding as an approach that results in few and more natural changes in the plant, when compared to the other techniques,".

Many respondents did not know how to deal with safety issues, like negative side effects or unacceptable long term effects. "People simply had no clue," said De Vriend, who was struck by the large amount of 'don't knows'. The survey also showed that the distinction between conventional plant breeding and other techniques is more important in the policy domain of access and innovation than the safety domain, which should be guaranteed in all cases. "People just think that all techniques should be properly regulated or safeguarded in terms of safety."

Session 4: Governance

The ruling of the EU Court of Justice about mutagenesis did not solve all the issues, and also increased the regulatory burden for breeding companies. In this session an analysis of the Court's decision is presented, followed by a three tier approach proposed by Norway and the discussion proposal of the Netherlands to exempt new plant breeding techniques that are at least equally safe as crops obtained by traditional plant breeding from GMO regulation. How to move forward?

A legal analysis of the EU Court's decision on mutagenesis (C-528/16)

Willem-Jan Kortleven, Assistant Professor at the Erasmus School of Law in Rotterdam, gave a comprehensive legal analysis of the ruling of the Court of Justice. He looked back at the history to find how the Court arrived at its judgement.

French activists demanded the revocation of a clause in the Environmental code that exempts products from obligations of the GMO Directive (2001/18/EC) and a ban on all herbicide-tolerant plant varieties obtained by mutagenesis. When the French government did not respond they turned to the highest administrative court in France (Conseil d'État). The Conseil, in turn, asked judicial questions to the European Court of Justice. One of the reasons was that they noted a discrepancy between the French law and Directive 2001/18/EC to the question whether mutagenesis constitutes GMO. Another reason was that the effects and risks of new directed mutagenesis resemble those of the transgenesis techniques. "The court's answer, as we all know now, was that organisms obtained by mutagenesis are GMOs within the meaning of the Directive 2001/18/EC. Only products of mutagenesis techniques *which have conventionally been used in a number of applications and have a long safety record* are exempt from obligations of the Directive," Kortleven said. "These criteria seem to restrict the scope of the exemption to mutagenesis techniques already in use before 2001."

Willem-Jan Kortleven, Assistant Professor at the Erasmus School of Law in Rotterdam

Kortleven tried to establish what the criteria "conventionally being used and having a long safety record" meant for exempting products of new mutagenesis techniques. Can new directed mutagenesis techniques ever fulfil these criteria? "There are two problems. First the use of the term conventional is conservative and seems to exclude the possibility that new techniques ever will fulfil these criteria. Is it imaginable that new directed mutagenesis techniques will turn in conventional? But then they need opportunity to develop and be used in order to become conventional. Same holds for having a long safety

record. A technique needs to have the opportunity to call itself safe, but will it get that opportunity as long as it has no long safety record. Here we have a catch 22 situation."

In conclusion, Kortleven made a tentative exploration which legal options for the development of gene editing there are left after this EU Court ruling. "The most frequently mentioned option is to revise the directive, if we want a future for gene editing in the EU. But it is by no means sure that current initiatives will find sufficient support." So what can we do in the meantime? "First it is important to acknowledge that not everything depends on bringing a product on the EU market. There are possibilities for universities and research labs of companies to employ research and development under contained use. Also field trials under national legislation by member states that are willing to support development of gene editing, could provide an opportunity for products of gene editing to be used in a number of applications and build on a safety record. And in that way fulfil the criteria to be exempt from the directive. If that is not accepted or sufficient, an admission procedure under the directive could follow, for example the procedure based on similarities between products of random and directed mutagenesis."

Norway: a novel tiered governance framework for GMO

The independent Norwegian Biotechnology Advisory Board has developed a novel governance framework with a more differentiated risk assessment, that can hopefully be adopted in the EU, said Sigrid Bratlie, senior advisor of the Board. "There is an urgent need for innovation in governance and a reframing of the public dialogue, now new breeding techniques give a much wider range of possible genetic changes and applications." "We think that this tiered system could solve one of the major problems of detection and labelling."

Sigrid Bratlie, senior advisor of the Norwegian Biotechnology Advisory Board

The proposed system consists of three tiers. "The first tier concerns genetically engineered organisms that have changes that exist or that can arise naturally. There is a notification system that is similar to Japan. The second tier concerns gene edits that are more complex, but are still within the species boundaries. It has an expedited assessment and approval system," explained Bratlie. The third tier concerns conventional transgenic organisms or organisms that contain non-existing and synthetic DNA sequences. They undergo the standard risk assessment and approval. The Norwegian model also offers scope for making the risk assessment procedure more dependent on aspects beyond health and commercial interests, such as social benefit, sustainability and ethics.

The Norwegian proposal was developed in close dialogue with the public. “Stakeholders within academia and industry organizations said that the framework lowered the hurdles to use these technologies sufficiently. It gave also more predictability in terms of product development and was more risk proportionate,” reports Bratlie. However NGOs and farmers organizations were concerned that there is still too little experience with these new technologies and the impact on ecosystems when rapidly developed products are introduced in large volumes. But there was also a lot of agreement among the stakeholder groups. All of them emphasize the value of having regulatory oversight and public trust. They also agreed that gene editing can contribute to sustainable agri- and aquaculture and emphasized the need for safeguarding health, environment, societal benefit, sustainability and ethics.”

“We think that our proposal offers all of these aspects, and is the way forward, also for the EU. We think that it is science based and risk proportionate. It will lower the regulatory hurdle for innovation sufficiently, it provides oversight and control. It also provides trust and transparency.”

Bratlie concluded by referring to what the Dutch minister said at the beginning of the symposium: “Safe innovation has contributed to feeding an increasing population for many years and will continue to do so, but it will also contribute to a shift towards a green economy and sustainable future if we use these technologies right.”

A discussion proposal for changes to the EU GMO directive’s exemption mechanism

In 2017 the Netherlands tried to reopen the policy discussion on regulation of new plant breeding techniques by putting a discussion proposal forward, explained Mijntje Aarts, Senior Policy Officer at the Directorate for Safety and Risks of the Dutch Ministry of Infrastructure and Water Management.

The discussion proposal outlined possible changes to the directive’s exemption mechanism in Annex IB from the GMO Directive. “Instead of listing techniques, we proposed to use criteria and thereby changing somewhat from a process to a product oriented approach with regard to exemptions. New techniques will be coming. We also focussed only on plants to keep the focus of the proposal small. The goal was to exempt non-transgenic plants that are at least equally safe as plants obtained by traditional breeding.”

This proposal was met with interest by the EC and member states. Although member states had not all the same view, they did feel that the directive was outdated and should be reviewed. But at the time they were mostly waiting for the EU Court’s decision on

Mijntje Aarts, Senior Policy Officer at the Directorate for Safety and Risks of the Dutch Ministry of Infrastructure and Water

mutagenesis techniques. When the Court decided in 2018 that products of new mutagenesis techniques are GMOs and fall under the scope of the GMO directive, many scientist and other stakeholders were very disappointed. “The ruling brought more legal clarity about the mutagenesis techniques, but also left other questions about other new plant breeding techniques and safety unanswered. Implicitly, the responsibility to address these questions was placed in the hands of the European legislator.”

In November 2018 an new advice of the Scientific Advice Mechanism followed. The advisors conclude that the GMO Directive should be revised to reflect current knowledge and scientific evidence. And also pleaded for a broad dialogue with relevant stakeholders and the public at large. In addition they also highlighted the issue of detection. Plants produced by NBT can enter the European market undetected which makes it hard to enforce the Directive. “We also see activities, innovation and companies are moving abroad.”

The Netherlands together with sixteen other member states, requested the incoming European Commission to put the adequacy of the European legislative framework for GMOs in their Work Programme. “However the Commission has not stated so far that they want to include it,” said Aarts. “But if they adhere to this request, we can submit the discussion proposal from 2017 again, depending on the course of the discussion. We see also a need for more harmonization of EU policy (medical applications). So depending on the discussions, we might call for a broader change of the legislation. Either way this will be a long term project.”

“Meanwhile technology does not stand still, science doesn't stand still, and so we will continue to lobby for revision of the GMO Directive to develop a future proof policy, and keep the door open for innovation and at the same time ensure safety.”

Discussion Session 4 & Concluding Remarks

The ruling of the EU Court of Justice gives member states some freedom to regulate exempted products. A member of the audience asked if Mijntje Aarts foresaw an amendment of the Dutch proposal from 2017, to not end up with a patchwork of different approaches of member states regarding those exempted products. “We want to table the proposal again, and take for instance into account the advice of COGEM this year to make the wording more specific and also look at the other proposals of Norway, Germany and France. We hope that by discussing our and other MS proposals to find a way forward to change the Directive and make it fit for purpose again,” Aarts answered.

William-Jan Kortleven was a bit sceptical, when asked for his opinion about the success of these proposals within the coming five years. As a lawyer he did not know how mutagenesis or gene editing is different from transgenesis, which might hold for some other member states too. “I think that will prove to be the biggest problem for getting these proposals through. The similarities with transgenesis are complicating the discussion.”

Another participant wondered if it is possible to change the Annex 1B now the Court of Justice has decided that targeted mutagenesis is GMO. Maybe other parts or the definition of GMO have to be changed too. Aarts agreed that the court’s ruling did not make revision easier, however it made very **clear that a policy debate is needed**. “We focused only on Annex IB, because if you want to change the actual definition of GMO, that would be a very long term process.”

It will take years before there is a workable situation. In the meantime innovation and science continue. Is there something that the EU could do, another participant asked, to make sure that we at least enable some of these benefits. Aarts was afraid that there was

not an easy way out of the deadlock that we are in. A member of the audience remarked in line with previous discussions: “first, we should get it on the agenda of the EC and then all invest in a good dialogue with the society and the commission about the proposal and that the impact assessment, which will be done, is reasonable and provides scope for good decision making. We know already from history how we ended up in overregulation.”

Chair Nico van Straalen and speakers Willem-Jan Kortleven, Sigrid Bratlie and Mijntje Aarts during a discussion on governance

A member of the audience noted: “we only have commercialized GM food crops with traits that impact and benefit all the farmers. We would never push crops with small traits through the regulatory system in Europe because we would never be able to earn a profit. For GMO we see the regulatory burden has gone up even though there is a kind of safety record. So **how do we ensure that our legislation is proportionate** for all categories of plants?”
Sigrid Bratlie pointed out that the Norwegian proposal with the different tiers in terms of risk assessments addresses this concern. “The expedited assessment that we propose on the second tier that could for example be that you get approval for a group of similar GMOs. A separate approval for each of them is not necessary, if there is no scientific based reason to do such a specific test. There is flexibility in the current Directive, but that is not used at the moment.” The questioner had to disappoint Bratlie, they did ask for that derogation from the requirements, but failed. “The commission continuously said that if it is in the legislation, it is not meant to derogate from.”

A broad dialogue **with stakeholders and the public at large,** was a call that was heard several times during this symposium. Huib de Vriend wondered if a real dialogue was possible if the positions are only black and white, yes or no GMOs. According to experience of Sigrid Bratlie a public dialogue can be actually quite constructive. “People are smarter than we give them credit for. I think if we are very specific about the benefits that the technology could provide for either them or the environment or animal welfare, it is possible to have a good discussion. We did that for our survey. There were many discrepancies, but they also agreed on many things which was very useful for us in shaping this proposal. And it had a lot of support from academia and industry and although there were concerns from NGOs and farmers, they also saw the value of these technologies. And now we are going forward in a more constructive manner.”

The **closing remarks** of professor Nico van Straalen of COGEM at the end of the meeting were hopeful. “We heard on the one hand an enormous disparity of approaches to deal with the issue. Some of them rooted in cultural traditions, others driven by economic circumstances. But we also saw a number of commonalities that we should foster. The product based and process based approaches that we thought were really very different are actually not so different after all.”

Van Straalen felt that “the times they are changing”, referring to a song he sang as a teenager. And he hoped that all the participants would one day look back upon this meeting and remember that that began on the 10th of October!

COMMISSIE GENETISCHE MODIFICATIE COGEM

Text: Astrid van de Graaf, science writer
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