Enabling genetic technologies for food security

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Summary

Increasing demand for food and feed in the context of a changing climate, accelerating biodiversity loss, declining arable land, and increased spread of agricultural pests and diseases has been described as 'a perfect storm'[1] that necessitates increased agricultural productivity. Crop genetic improvement is crucial to address this challenge. The last 50 years have seen extraordinary advances in our understanding of plant genes and genomes. These developments underpin a highly productive plant breeding industry and also guide the work of those improving crop traits by both breeding and gene editing. In the context of gene editing, the UK government has recognised the need for regulations to keep pace with technology development by passing the Precision Breeding Act, which creates a path for crops improved with genetic technologies to be brought to public use.

The crop improvement method that has come to be known as genetic modification (GM) can deliver outcomes that other crop breeding technologies cannot. For example, genes for useful immune receptors that confer disease resistance can be identified in wild relatives and brought into the genetic background of a favoured crop variety, without introducing other, potentially deleterious, genes. In recognition of this, and of the extensive evidence that there is nothing risky about the technology *per se* (risk and benefit are instead determined by the purpose for which the method is used), a growing number of countries are using the GM method for crop improvement to help meet their food security needs.

Given the UK's academic plant science and commercial plant breeding expertise, the country has a great opportunity to use the GM method for the benefit of its citizens, to reduce the environmental and biodiversity impact of agriculture and to enhance international food security. UK plant science innovations are already being commercialised in other countries with more proportionate regulatory regimes. Outside the EU, the UK is no longer bound by an approach to regulation that is based on the scientifically unjustified idea that there are intrinsic risks in using the GM method. Instead, it can take advantage of the experience of 30 years of commercial use of GM crops to ensure its regulatory processes are proportionate to the potential for risks of specific traits in individual organisms, rather than the technology that delivers those traits. Using the GM method has the potential to decrease the land required to meet our food needs and so free up more space for nature, decrease our dependence on food imports and our reliance on agrichemicals, and so decrease the economic and environmental costs of food production.

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[1] Beddington J. 2009 *Food, Energy, Water and the Climate: A Perfect Storm of Global Events?* Government Office for Science, London.

We recommend the UK Government re-evaluate the content and implementation of the legacy EU regulations that govern crops improved with the GM method and that were incorporated into UK law. These regulations have been implemented in the EU in a manner that prevents publicly funded discoveries from resulting in valuable innovations. Proportionately implemented regulation should be based on hypothesis-driven risk assessment of the specific properties conferred by each introduced trait, the intended use and the receiving environment.

In the immediate future, even without primary legislation, the transposed regulations enable developers of GM traits to make an application for regulatory approval that does not contain all the studies that are routinely required in the EU, if there is a sound case for not including them (a full description of how this approach could work in practice is included in section 3.3). UK regulators should be open to applications that carry such requests, especially where the crop has already been approved by a trusted regulator in another country. In the longer term, the UK government should follow its own policy on regulation as set out by the 2023 Science and Technology Framework and look to adopt an outcomes-based approach that stimulates demand for science and technology while safeguarding citizens.

Proportionately implemented regulation would open up opportunities for new start-up companies to turn the plant science advances of the last 30 years into valuable innovations and products. This would capitalise on the opportunity provided by the greater accessibility of the technology now that many of the patents that previously restricted access have expired. Spurning the use of GM creates a substantial, and avoidable, opportunity cost.

Introduction

Agriculture faces significant challenges. The global food system is the major cause of the biodiversity crisis and contributes approximately one third of the greenhouse gas emissions that are driving the climate emergency[2]. At the same time, food supply is threatened by the biodiversity and climate crises, degradation or loss of arable lands, and increased competition for land from uses such as carbon sequestration and nature restoration. Without systemic changes, increased demand for food from a growing and increasingly affluent global population will exacerbate agriculture's contribution to biodiversity loss and vulnerability to climate change.

Many initiatives have sought to address these challenges. Policy interventions such as England's Environmental Land Management Schemes, the US's Inflation Reduction Act, and the EU's Farm to Fork Strategy have a common goal of reducing the environmental impact of food production. The Farm to Fork strategy, together with independent reports such as the UK's *National Food Strategy* or the EAT-Lancet Commission on *Healthy Diets from Sustainable Food Systems*, also consider questions of consumption, particularly what constitutes a healthy and sustainable diet, alongside questions of production. All these initiatives share a diagnosis of the problem but there is less consensus on the solutions.

This report argues in favour of better regulating a technology that could contribute much more to addressing these challenges. The well characterised GM method[3] enables plant breeders to capitalise on the advances in genetics of the last 50 years and helps them produce crop varieties that reduce the environmental impact and increase the resilience of agriculture whilst also producing more nutritious food.

This report does not explore complementary solutions such as reducing food waste or changing diets (including consumption of alternative proteins such as products derived from the contained use of GM micro-organisms), except to note that these paths are also important and should not be seen as competing alternatives. Diet-related health issues, such as diabetes and obesity, are also out of scope. The report's focus is on the potential opportunities from cultivating GM crops in the UK. It does not consider imports of GM foods but acknowledges that it would not make sense to apply more stringent regulation to imports than are applied to home grown crops.

Regulation has an important role to play in maximising the potential benefits of new products and technologies whilst minimising risks. To over-emphasise potential risks is likely to limit the benefits whilst under-emphasis means genuine risks could be insufficiently controlled. Regulators must strike the right balance between managing risk and realising benefits based on the available evidence. In the early days of commercial use of the GM method it was reasonable to err on the side of managing risk given the prevailing uncertainty about the technology. Subsequent regulatory experience with GM crops means there is now extensive evidence on actual benefits and risks that justifies re-evaluating whether current regulatory systems deliver the optimum balance. Given the impacts of current agricultural practices and the

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[2] IPCC. 2019 Summary for Policymakers. In: Climate change and Land: an IPCC special report on climate change, desertification, land degradation, sustainable land management, food security, and greenhouse gas fluxes in terrestrial ecosystems. Shukla PR *et al*. (eds). 2019. (online) Available at: https://www.ipcc.ch/srccl/chapter/summary-for-policymakers/ (accessed 23 July 2023).

[3] This report uses the term 'GM method' even though several methods exist that can be used to transfer DNA into a plant cell. Nearly all commercial lines carrying GM traits have been created using the natural mechanism of Agrobacterium-mediated DNA delivery. It is also possible to deliver DNA by bombardment of plant cells with gold nanoparticles loaded with plasmid DNA, or by introducing plasmid DNA into plant protoplasts using polyethylene glycol or electroporation. For this report, any transfer of DNA that derives from another organism and does not depend on a site directed nuclease is referred as an example of using 'the GM method', which usually involves use of Agrobacterium.

potential of GM to reduce these, this re-evaluation should consider the relative merits of adopting a specific implementation of the technology or of rejecting it and maintaining the *status quo*.

Before delving into these arguments, it is worth stating several assumptions that underpin this report's analysis. Firstly, the report assumes that the crop species currently grown in the UK will remain broadly the same, at least for the next few decades. Secondly, these crops will need protection from weeds, pests and diseases and will require supplementary nutrition with key minerals such as nitrogen, potassium and phosphorus.

The first section of this report reviews various methods underpinning crop improvement. Traditional plant breeding has already made, and continues to make, major contributions to increasing yields; it is estimated that plant breeding underpinned 88% of yield increases in UK wheat between 1948 – 2007[4]. However, the genetic modification ('GM') method, in which genes are transferred between species, can achieve useful outcomes that would be hard or impossible to achieve with plant breeding or even with gene editing methods, in which small changes are made at defined locations in the genome.

The second section considers why crops improved with the GM method are regulated differently to those resulting from other breeding technologies and the deterrent effect this has had on GM investment and innovation. It demonstrates that extensive experience of safety, efficacy and effectiveness of the GM method over the last 30 years suggests the approach to regulation developed in the 1990s is no longer justified.

The third section presents ideas for how the UK could apply the current regulatory framework in a manner that is aligned with the high-level strategy for regulation set out in the Government's Science and Technology Framework by being proportionate to the known risks of GM crops.

Under the proposed approach, regulators would focus on risks for which there is a plausible causal mechanism and would confine requirements for extensive data provision to species, traits, or biological mechanisms for which there is little prior regulatory experience.

The fourth section sets out a vision for the future of regulation for genetic technologies. This would focus on the outcome that has been achieved rather than the genetic technology used. This approach would encourage innovation by ensuring regulation keeps pace with technology development.

Whilst a more enabling approach to regulation in the UK is a necessary condition for ensuring that crop improvement using the GM method can play its part in addressing the challenge of sustainable food supply, it is not the only consideration. Navigating discrepant regulation between jurisdictions creates an additional challenge for whether promising varieties with GM traits are adopted by industry and translated into new crop varieties. Any food product that is exported must comply with the regulations of the jurisdiction that is importing it. In the UK context this is particularly relevant to those crops, such as wheat, that have significant export markets, especially to the EU. Other crops, such as potatoes or tomatoes, are produced primarily for consumption in the UK. Producing GM varieties of these crops would still require provenance tracking to ensure the products do not end up in jurisdictions where approval has not been granted.

Given the UK has already chosen to diverge from the EU in regulating gene editing, it should not be deterred from also regulating the GM method in a way that enables use of the technology to help address the many challenges of sustainable food production and consumption.

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[4] Mackay M, Horwell A, Garner J, White J, McKee J and Philpott H. 2010 *Reanalysis of the historical series of UK variety trials to quantify the contributions of genetic and environmental factors to trends and variability in yield over time*. Theoretical and Applied Genetics 122, no. 1: 225-238. doi:10.1007/s00122-010-1438-y.

Why use the GM method for crop improvement?

Section summary

The process of genetic modification (GM), in which genes are moved between species, fits within a long history of breeding crop plants from their wild ancestors and with recruiting useful genetic variation into crop plants from their wild relatives. The GM method is one of several useful technologies for developing improved crops that address a wide variety of agricultural challenges. Concern that there might be something uniquely risky about the GM method led to the first risk assessment requirements for new GM crop varieties. Section 3 discusses the history of GM regulation in the UK and EU, deployment of the technology, and crops that have been or are being developed.

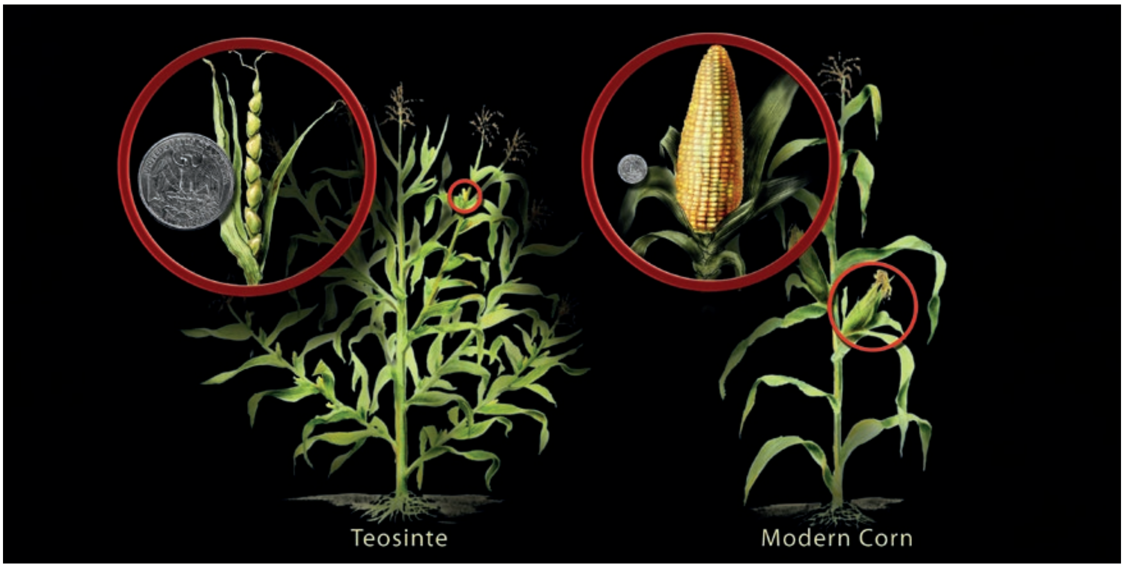
1.1 Genetic modification in agriculture has a long history

Selective breeding and mutation breeding

Humans have long made choices that changed the genetic composition of the plants in our diet. Selection for size and yield of grains and fruits, taste, resilience to frost, drought or disease, or plant architecture that is well adapted to cultivation or harvest have all led to differences between the traits and DNA sequences of modern crops and those of their wild ancestors.

Following Gregor Mendel's work in the 19th century on patterns of inheritance of plant traits, in the early 20th century desirable characteristics in crops were also found to be heritable. This understanding led to the first efforts to increase crop genetic variation using 'mutation breeding'. This involves exposing plant tissues to chemicals or radiation to increase mutation rates in the hope of selecting some mutations that result in useful traits[5]. Many crops grown today, including in organic agriculture, carry traits that resulted from use of this method.

The success with which plant breeding was used for crop improvement was accelerated by the emergence in the 1990s and 2000s of technologies such as positional cloning and genome sequencing that helped to link specific traits to specific variants of specific genes. This progress in understanding crop genetic variation continues to underpin plant breeding for improved crop productivity and other traits.



Right
Illustration showing the difference between modern maize and its wild ancestor, teosinte. Selective breeding over thousands of years favoured plants with fewer branches and so fewer but larger ears of corn. Modern maize has also lost the hard casing that covered each kernel in teosinte. Credit: Nicolle Rager Fuller, National Science Foundation.

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[5] Agar J and Ward J, eds. 2018 *Histories of Technology, the Environment and Modern Britain*. London: UCL Press.

Transgenic crops (1980s – today)
The ability to link specific genetic variants to specific traits, combined with the discovery in the 1970s of how the bacterial plant pathogen *Agrobacterium tumefaciens* naturally delivers DNA into plant cells, enabled scientists since the early 1980s to use Agrobacterium to deliver any gene(s) of interest. The plants that received genes using this method ('transgenic' plants) came to be known as 'Genetically Modified Organisms (GMOs)', despite the fact that the varieties into which genes are inserted are already genetically modified compared with their wild ancestors. The idea that there is something unique about these transgenic crops is made even less plausible by emergent evidence that current commercial varieties of both sweet potatoes[6] and wheat[7] contain genes from other species due to processes of horizontal gene transfer thousands of years ago.

The GM method inserts DNA into the genome at random locations. Insertion events can be accompanied by unintended genetic changes. Scientists using the method therefore screen multiple independent transgenic plants carrying distinct insertion events and take forward the ones where the introduced genes robustly express the trait of interest and there are no unintended disruptions to other genes or other genetic changes. DNA sequencing can now be used to ensure the only change is the insertion of intended genes.

The GM method has been widely adopted in plant science since 1983 and the first transgenic crops entered commercial cultivation in the 1990s. One of the first applications of the GM method resulted in crop plants with increased insect resistance, by expressing an insecticidal *Bacillus thuringiensis* crystal protein (Bt) that acts against the larvae of insects that eat the crop. *B. thuringiensis* is a bacterium whose spores contain Bt protein and are widely used for insect control in organic agriculture. During 1996 – 2020, Bt maize reduced insecticide use by 85,000 metric tonnes (a reduction of 41% of all pesticides used on the crop) and Bt cotton by 339,000 metric tonnes[8] (equivalent to roughly 30% pesticide usage on cotton by volume). The introduction of Bt maize also had a human and animal health benefit as reduced damage by insects led to reduced colonisation by mycotoxin-producing *Aspergillus* and *Fusarium* fungi and so reduced levels of toxins produced by these fungi in the corn cobs[9]. Other implementations conferred herbicide resistance, which enabled easier weed control and facilitated both no-till agriculture and a method for easier hybrid seed production, allowing capture of the yield advantage that results from hybrid vigour. A more extensive account of additional implementations of the GM method can be found in Annex A.

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[6] Quispe-Huamanquispe D G, Gheysen G and Kreuze J F. 2017. *Horizontal Gene Transfer Contributes to Plant Evolution: The Case of Agrobacterium T-DNAs*. Frontiers in plant science, 8, 2015. https://doi.org/10.3389/fpls.2017.02015

[7] Wulff B B H and Jones J D G. 2020. *Breeding a fungal gene into wheat*. Science (New York, NY), 368(6493), 822 – 823. https://doi.org/10.1126/science.abb9991

[8] Graham Brookes. 2022 *Genetically Modified (GM) Crop Use 1996 – 2020: Environmental Impacts Associated with Pesticide Use Change*. GM Crops and Food, 13:1, 262-289, DOI: 10.1080/21645698.2022.2118497

[9] Carzoli A, Aboobucker S, Sandall L, Lübberstedt T, Suza W. 2018. *Risks and opportunities of GM crops: Bt maize example*. Global Food Security. 19. See: 84-91. 10.1016/j.gfs.2018.10.004

BOX 1

The Puzstai scandal, public attitudes and GM regulation

In the 1990s, the first GM food – a tomato paste – was sold in the UK. Consumers bought over 1.8 million cans of this GM paste when it was sold alongside its conventional equivalent but at a cheaper price and it initially outsold the non-GM variety by a ratio of two to one. However, sales declined dramatically after high-profile claims by Dr Arpad Puzstai at the Rowett Research Institute that rats fed on GM potatoes had worse health outcomes than rats fed on non-GM potatoes. It subsequently emerged in a House of Commons Select Committee enquiry that "Dr Pusztai's experiments involving GM material were incomplete and the Rowett Research Institute's press release had misreported the scientific findings of the experiments"[10]. Dr Pusztai himself told the enquiry that his research found "no differences between parent [the potatoes whose genome was modified to create a GM variant] and GM potatoes", directly contradicting his and his institute's previous claims. This was corroborated by an independent statistical analysis commissioned by Dr Puzstai that did not support his conclusions and questioned the validity of the study design.

Nevertheless, the publicity generated by this research helped entrench a public perception that GM foods are unsafe, and led retailers to commit to removing GM crop products from their product ranges.

Public concerns were driven by more than just questions of safety. For example, the first GM crops, particularly soybeans and maize, were imported into Europe from the US for use as animal feed. As people could not tell whether or not the meat they were buying came from an animal fed with GM crops, this raised questions about transparency and consumer choice, particularly for those who wanted to reject the technology. The fact that these crops were often modified to be resistant to herbicides made by the same companies as were selling the GM seeds contributed to concerns about increasing concentration of corporate control of agriculture. This was compounded by the fact that these companies and chemicals were associated with food production systems that are based on monocultures and appear to ignore wildlife and the maintenance of soil quality. The distinct issues of the intrinsic safety or otherwise of the GM method and the uses to which it was put were often conflated.

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[10] House of Commons Science and Technology Committee. 1999 Scientific Advisory System: Genetically Modified Foods (online). Available at: https://publications.parliament.uk/pa/cm199899/cmselect/cmsctech/286/28605.htm#n45 (accessed 20 July 2023).

When the method was first deployed, there were concerns that use of the GM method per se might lead to unpredictable risks resulting in undesirable side effects either for human health or for the environment. These concerns led to the first regulations requiring extra risk assessments of new plant varieties with GM methods in their pedigree. As will be discussed in Chapter two, the way these regulations have been implemented by the European Union, especially the need for approval of any GM crop by the European Commission and Member States after scientific evaluation by the European Food Safety Authority (EFSA), led to the effective prohibition of cultivation of GM crops in member states, with the exception of GM insect resistant maize, which is widely grown in Spain and Portugal.

As well as effectively prohibiting the cultivation of GM crops, there is some evidence that the EU's approach to regulation has reinforced negative attitudes towards the technology[11]. In a 2019 UK Government-commissioned survey of public attitudes to science, of the 73% of respondents that felt at least to some extent informed about GM crops, 36% felt the benefits of GM crops outweigh the risks compared with 32% that felt the opposite[12]. Although attitudes were more positive among people who felt more informed about the technology (46% vs 30%), these results suggest widespread ambivalence at best when considering GM crops in the abstract. However, this survey also included questions about specific applications for gene editing. Among the most popular applications were making vegetables disease resistant (63% support vs 22% opposed), increasing the health benefits of vegetables (56% vs 26%), and increasing vegetable production (55% vs 27%).

Although these results relate to gene editing rather than GM, they echo the results of public attitude research commissioned by the Royal Society in 2017 which found that the purpose for which genetic technologies are used makes a significant difference to whether that application is viewed positively or not[13]. This suggests that the social licence for GM crops will be strongly influenced by the traits they have been modified with. It is therefore significant that, as discussed in Section 1.3 and Annex A, many of the traits that have been commercialised in recent years, or are close to commercialisation, provide improved resistance to pests and diseases, more nutritious food, or maintain or enhance productivity in the context of a changing climate.

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[11] Department for Business, Energy and Industrial Strategy. 2020 Public Attitudes To Science 2019, BEIS Research Paper Number 2020/012. Available at: https://assets.publishing.service.gov.uk/media/5f22cf7bd3bf7f1b1593c15c/public-attitudes-to-science-2019.pdf (accessed 19 October 2023).

[12] *Ibid*.

[13] Van Mil A, Hopkins H and Kinsella S. 2017 *Potential uses for genetic technologies: dialogue and engagement research conducted on behalf of the Royal Society*. London: Royal Society. https://royalsociety.org/~/media/policy/projects/gene-tech/genetic-technologies-public-dialogue-hvm-full-report.pdf

Gene editing (2000s – today)
Changes can be made at precise genomic locations using programmable Site-Directed Nucleases (SDNs)[14]. The widely adopted CRISPR/Cas SDN systems were first described in 2012[15]. Gene editing can either result in simple mutations at defined loci (SDN1), the introduction of a few specified nucleotides at a defined location (SDN2) or the introduction of a gene or genes at a defined location (SDN3).

The development of SDN1 and SDN2 gene editing tools challenged the interpretation of the scope of the regulatory framework for GM crops, because these editing tools could be used to make genetic changes – disrupting genes or converting a gene from one variant to another – that were indistinguishable from those found in conventional breeding. This led to a long period of regulatory uncertainty in the EU while the Court of Justice of the European Union (CJEU) adjudicated a case on the scope of the mutagenesis exemption in the GMO Directive. The Court confirmed in 2018 that organisms developed through mutagenesis by gene editing are regulated as GMOs, and that only organisms developed through mutagenesis techniques developed before 2001 were exempted from the GMO Directive.

The European Commission interpreted the 2018 CJEU ruling to mean that all gene edited organisms are GMOs, counter to the trend in most other jurisdictions, which have amended their GMO regulations since the emergence of gene editing.

Japan is one of these countries and the first gene-edited crop made with CRISPR/Cas was released commercially there in 2021. England joined the growing group of countries that have amended their regulations to exempt at least some genetic technology products from their GM regulatory frameworks with the 2023 Genetic Technology (Precision Breeding) Act. At the time of writing, secondary legislation is being developed that will determine the regulatory requirements for products that fall within the remit of the Precision Breeding Act.

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[14] Kim Y G, Cha J and Chandrasegaran S. 1996 *Hybrid restriction enzymes: zinc finger fusions to Fok I cleavage domain*. Proceedings of the National Academy of Sciences 93, no. 3: 1156-1160. doi:10.1073/pnas.93.3.1156.

[15] Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna J A and Charpentier E. 2012 *A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity*. Science 337, no. 6096 (2012): 816-821. https://doi.org/10.1126/science.1225829

1.2 Current GM regulation and cultivation

The Genetic Technology (Precision Breeding) Act created a new regulatory entity – the Precision Bred Organism (PBO). A PBO is a plant or animal whose DNA has been modified using a genetic technology but with a type of genetic change that could have occurred 'naturally' and been selected in a 'traditional breeding' programme[16]. Whether a specific genetic technology product is classified as a PBO will be determined by an expert advisory committee but is likely to exclude any genetic changes that involve the movement of genes between species that cannot be inter-crossed. Organisms that do include genes from a sexually incompatible species are likely to remain regulated as GM crops. Notably, the Advisory Committee on Releases to the Environment (ACRE) guidance defines a category of 'cis-genic' plants, for which the GM method has been used to deliver genes that could have been crossed in by traditional genetic methods, but that can still be classified as Qualifying Higher Plants and potentially as PBOs[17]. ACRE is the panel of independent scientists that provides statutory advice to ministers in the Department for Environment, Food and Rural Affairs on the potential environmental and health risks of genetically modified organisms.

In passing this legislation, the Government emphasised that genetic technologies such as gene editing have the potential to achieve desirable plant breeding outcomes (such as reduced dependence on synthetic pesticides and fertilisers) faster and more cheaply than traditional breeding approaches. This is because a desirable characteristic can be introduced directly into an elite breeding line (the plants from which breeding companies generate seeds and sell for cultivation) without having to subsequently breed out any undesired characteristics, as required when carrying out standard back-crossing programmes.

However, in emphasising the value of gene editing methods to change genes within a species, the legislation has not addressed the potential value for crop improvement of using GM methods to move genes between species. By justifying the proposed changes on the basis that Precision Bred Organisms are not the same as Genetically Modified Organisms[18], the Government left unchallenged the false notion that use of the GM method *per se* creates novel health or environmental risks. This policy fails to recognise that many desirable crop characteristics are much more effectively achieved by moving genes between species. As Box 2 shows, a growing number of countries are approving GM crops.

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[16] In the Precision Breeding Bill, traditional breeding is defined as: (i) sexual fertilisation, (ii) spontaneous mutation, (iii) in vitro fertilisation, (iv) polyploidy induction, (v) embryo rescue, (vi) grafting, (vii) induced mutagenesis, or (viii) somatic hybridisation or cell fusion of plant cells of organisms which are capable of exchanging genetic material by a process within sub-paragraphs (i) to (vii).

[17] Advisory Committee on Releases to the Environment (ACRE). 2022 *Technical guidance on using genetic technologies (such as gene-editing) for making 'qualifying higher plants' for research trials*, UK Gov (online). Available at: https://www.gov.uk/government/publications/acre-guidance-on-genetic-technologies-that-result-in-qualifying-higher-plants/technical-guidance-on-using-genetic-technologies-such-as-gene-editing-for-making-qualifying-higher-plants-for-research-trials (accessed 11 July 2023).

[18] Department for the Environment, Food and Rural Affairs (DEFRA). 2023 *Genetic Technology Act key tool for UK food security*, UK Gov (online). Available at: https://www.gov.uk/government/news/genetic-technology-act-key-tool-for-uk-food-security#:~:text=The%20Genetic%20Technology%20(Precision%20Breeding,leader%20in%20agri%2Dfood%20innovation (accessed 28 April 2023)

BOX 2

Growing global adoption of GM crops.

GM crops were grown in 27 countries in 2021, with the greatest uptake in the Americas. Since 2014, more than 90 percent of US corn, upland cotton, and soybeans carried GM traits[19]. As will be discussed, the EU has a restrictive approach to regulation that has influenced the approach taken in other parts of the world, particularly sub-Saharan Africa. However, a growing number of low- and middle- income countries are now using the GM method to help address the challenges of agricultural pests and climate change. Argentina has developed a drought-resistant wheat by using a regulatory gene (known as *HB4*) from sunflower. In 2019 Nigeria approved the commercial cultivation of a GM variety of cowpea (black-eyed bean, *Vigna unguiculata*) that is resistant to the bean pod borer, an insect pest that can cause yield losses of up to 80%.

In 2022 Kenya reversed a decade-long ban on the cultivation of GM crops with a view to approving maize that is resistant to both drought and to fall armyworm, a crop pest that was first reported in Africa in 2016 and that can devastate maize crops. In southeast Asia, farmers in Bangladesh have since 2013 been growing Bt brinjal (aubergine) that carries a Bt gene that confers resistance to fruit and shoot borer pests. This has greatly reduced losses to these pests and also reduced farmer exposure to, and environmental damage from, insecticide sprays. Bt Brinjal was also approved in the Philippines in 2022. In India in 2022, the government gave the first ever approval for environmental release of a GM *Brassica juncea* (oilseed mustard) food crop that had been engineered to facilitate hybrid seed production, enabling increased yields. In 2021, Brazilian public sector scientists developed and brought to market a bean that is resistant to bean golden mosaic virus[20]. Many more GM crops are under development by scientists in these regions to help address local agricultural challenges.

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[19] Economic Research Service US Department of Agriculture. *Recent trends in GE adoption* (online). Available at: https://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-u-s/recent-trends-in-ge-adoption/ (accessed 17 October 2023)

[20] Norero D. 2021 *The story behind the $100 public GM bean that reaches Brazilian plates*. Genetic Literacy Project (online). Available at: https://geneticliteracyproject.org/2021/08/31/the-story-behind-the-100-public-gm-bean-that-reaches-brazilian-plates/ (accessed 11 July 2023).

1.3 Selected practical applications of the GM method

As discussed in the introduction, human civilisation faces the significant challenge of producing more nutritious, affordable food, using fewer synthetic inputs and less land, despite climate change causing increasingly frequent extreme weather events, accelerating land degradation and changing patterns of pests and diseases. The GM method is already being used commercially in many countries to develop improved crops that help societies to meet this challenge. Unless specified otherwise, all of the examples included below have already been commercialised or have been shown to function in the relevant crop species and so could be commercialised relatively swiftly. Detailed discussion of all these examples and others, with citations, can be found in Annex A.

GM for diseases, pests and weed control

GM provides an opportunity to move plant immune receptors that have evolved in wild crop relatives into crop species, protecting against the estimated $290 billion of crop losses caused by pests and diseases. Examples of this include potatoes that are resistant to the blight that caused the Irish potato famine, resistance to viruses that are spread by aphids in a range of plants, resistance to wheat rusts and resistance to the *Ralstonia solanacearum* bacterium that causes bacterial wilt in crops such as potatoes, tomatoes and aubergines. Insect resistance conferred by *Bacillus thuringiensis* (Bt) crystal proteins continues to reduce the need for insecticides in cotton, maize and aubergine and could provide benefits in many other crops. More controversially, the GM method has been used to confer herbicide resistance to crops, facilitating weed control and also enabling a process for hybrid seed production.

GM for improved mineral nutrition and enhanced photosynthesis

The production and application of synthetic inputs such as pesticides, herbicides and inorganic fertilisers contribute to both global and local environmental problems, through greenhouse gas emissions, and soil compaction from tractor journeys, disruption of the soil microbiome and pollution of water courses. GM is being used to make cereal varieties that absorb nutrients more efficiently, crops that can be fertilised with phosphites rather than phosphates thus reducing the need for herbicides and crops with increased yield potential because they photosynthesise more efficiently. Increased yields could reduce the land required for food production and so provide more space that is dedicated to nature. In the longer term, genes that confer the ability to form nitrogen-fixing associations with *Rhizobium* bacteria are being moved from legumes to non-legumes such as cereals, which would greatly reduce the need for nitrogen fertilisers.

GM to increase resilience to climate change

The climate crisis is leading to increasingly frequent weather events that current crop varieties struggle to cope with. A particular concern is heat and drought. Argentinian scientists have developed a more drought tolerant GM variety of wheat using a gene from sunflowers and they hope to licence the technology to other plant breeders to develop drought-tolerant varieties of other crops.

GM to increase nutritional content of foods

Millions of people worldwide suffer from diseases caused by nutrient deficiencies because they cannot afford sufficiently varied diets to meet their nutritional needs. Increasing the nutrient content of the staple foods that comprise a large part of nutrient-deficient diets can help address this. 'Golden Rice' enriched with beta-carotene to address Vitamin A deficiency is the most high-profile example of this approach but scientists are also working on wheat with increased levels of iron and zinc. Away from staple foods, other GM projects have developed vegetable oil that is rich in essential long chain omega-3 fatty acids and tomatoes with increased polyphenols, which are associated with reduced risk of certain cancers and cardiovascular disease.

GM to remediate contaminated land

Given the many pressures on land use, there is growing concern about the amount of land contaminated with toxic chemicals from sources such as mining, heavy industry or military conflict. Phytoremediation – using plants to clean up contaminated land – could be a more cost effective and less environmentally damaging approach than current alternatives. Scientists are using the GM method to develop plants that can remediate a wide range of chemicals, increasing the feasibility of this approach.

1.4 Business and economic development opportunities from proportionate regulation

Better regulation of crops carrying GM traits would realise benefits for both producers and consumers in the UK. The UK's publicly funded, world-leading plant researchers and research institutes have made valuable discoveries and innovations that cannot be commercialised here if we continue to implement GM regulations in the same way as the EU. Several such discoveries already have been, or are in the process of being, commercialised in countries with more proportionate regulatory regimes, particularly the US. The purple tomato developed by the John Innes Centre and taken forward by Norfolk Plant Sciences is approved and is already being grown and sold in the US. Genes for potato late blight resistance identified by The Sainsbury Laboratory, Norwich are already commercialised in the US by Simplot Inc, and would reduce fungicide spraying of potato if commercialised in the UK. Production of *Camelina sativa* oilseeds developed by Rothamsted Research to be enriched with the long chain omega-3 fatty acids DHA and EPA (which are thought to be conducive to improved heart health) is currently being scaled up in preparation for commercial release in the US in collaboration with Yield10 Bioscience.

All of these examples could form the basis of a thriving business if commercialised in the UK. This would help attract further funding and investment to develop the UK's plant science and commercial breeding sectors and thus re-establish Britain as a global hub for crop improvement research and innovation. The pace of developing this new industry could be accelerated by deploying technology validated elsewhere to target pests that are a particular problem in the UK. For example, using the Bt proteins discussed above could control pests such as larvae of the flea beetle or the cabbage white butterfly, and so replace the pesticides used by both commercial and domestic growers.

Should initial attempts to commercialise established traits be successful, there is a substantial repertoire of traits with credible prospects for improving crops whose development has been paused due to uncertainty about both the regulatory process and public demand for GM food. There is a particular opportunity to develop combinations of traits, such as stacking enhanced photosynthetic efficiency with omega-3 production for example. If developed and validated in the UK, they then could be sold in much larger markets such as the US and Canada. This industry would need time to grow – crop improvement plays out over long timescales – but there will be a greater opportunity for UK businesses in global markets if they have a supportive policy framework in their home market.

Taking advantage of the GM method

These examples demonstrate the way the GM method can enhance current crops, which themselves result from millennia of selective breeding. Using the method, breeders can access a much greater range of genetic variation and are no longer confined to genes for traits, such as disease resistance, that are only available in the species they are working with. GM approaches to many of today's challenges are faster and more durable than traditional breeding methods. Many objectives, such as moving immune receptors between sexually-incompatible species, nitrogen-fixing cereals or enhanced photosynthesis, cannot be achieved without GM.

Those countries that have made greater use of the technology have done so through an enabling regulatory framework. The EU's framework (which has been transposed into UK law), has historically proved a barrier to realising the social, economic and environmental benefits of using the GM method for crop improvement. The next sections discuss why the EU framework has proved to be a barrier and what the UK could do to take a more proportionate approach.

Plant breeding regulation and current GM crop regulation

Section summary

The previous section highlighted some of the ways other countries are capitalising on the opportunities of GM for consumers, farmers and the environment. It also highlighted the divergent approach to regulating GM compared with other plant breeding technologies. This section explores the way traditional plant breeding technologies are regulated and contrasts this with the additional requirements for GM crops. It demonstrates that the EU's approach to regulating GM crops, now transposed into UK law, has not kept up with current understanding of possible risks associated with using the technology. This has deterred investment in the technology and hindered realisation of public benefits.

2.1 Authorisation process of non-GM crops

Before commenting on the extra scrutiny to which GM crops are subjected, it is important to understand the evaluation process for all new varieties that derive from conventional breeding, including mutagenesis. All breeding processes, whether GM or not, have the risk of introducing unwanted genetic changes that could limit the agricultural utility of a new crop variety. For this reason, robust procedures assess whether a new variety produced by a plant breeding company becomes approved for agricultural use by being added to the National List (NL) and then the Recommended List. The performance of any such new variety is assessed in multiple locations, in multiple years, in comparison to varieties that are already approved.

Any new variety must show Distinctness, Uniformity and Stability (DUS). These requirements ensure that varieties can be distinguished from each other, that all plants derived from planting any variety are the same and that the properties of a variety are indistinguishable through multiple generations. For example, for wheat, breeders will typically assess an aspiring new variety over 5 years internally before submitting to NL trials. These NL trials are then conducted over 2 years at 6 locations.

National Listing also involves trials to establish a candidate variety's Value for Cultivation and Use (VCU). This provides an independent assurance that only varieties with improved performance or end-use quality are approved for marketing to, and thus planting by, farmers. If new varieties pass both DUS and VCU evaluations, they are entered onto the National List, a legal requirement for selling the variety for agricultural use. Once on the National List, the new variety can be submitted to recommended list trials, which helps with marketing a successful variety (although not a legal requirement, more than 90% of the wheat grown in the UK are Recommended List varieties). These involve evaluating varieties at 25 locations, testing all traits, and this trialling continues so long as a variety is on the recommended list. This assessment will also be conducted for any proposed new variety that has been developed with the GM method. Thus, any off-target effects from using GM (or indeed gene editing) that could have deleterious consequences will be eliminated during standard varietal evaluation. Although none of these requirements assess risks to human health or the environment, there is no evidence that the lack of such requirements has led to demonstrable harms.

2.2 Additional risk assessment of GM crops

Before they can be submitted to the National List process, GM varieties have to be assessed for risks to the environment and human health. Risks to the environment and possible health effects of environmental exposure are assessed by the Advisory Committee on Releases to the Environment (ACRE). If the GM crop is intended for human consumption, any potential risks to human health are assessed by the Advisory Committee on Novel Foods and Processes on behalf of the Food Standards Agency (FSA).

Any GM crop that has been approved and is being cultivated is also subject to Post-Market Environmental Monitoring to control for any specific risks identified in the risk assessment process (case specific monitoring) and any unforeseen harms (general surveillance). The developer of the GM crop is responsible for this monitoring.

If the rules inherited from the EU continue to be applied in the same way in the UK, it will result in these risk assessments being applied in a manner that is disproportionate to the risks of individual GM crops.

2.3 Disproportionate requirements of current GM crop regulation

Until the UK left the EU at the beginning of 2020, its approach to regulating Genetically Modified Organisms was set by its EU membership. Since then, the legislative framework has remained the same but the ultimate arbiter of the regulations on environmental risk assessment has moved from the European Commission to the Secretary of State at the Department for the Environment, Food and Rural Affairs, and for food safety, to the FSA. As will be discussed in Chapter 3, this is significant as the wording of the legislation allows for flexibility in how these regulations are applied, enabling the UK to take a more case-by-case approach to any potential risks of crop varieties with GM traits than was the case when it was a member of the EU.

The approach taken by the EU has been criticised by ACRE. In a series of reports in 2013[21], ACRE identified shortcomings in the EU's approach to the environmental risk assessment of GM crops and highlighted the consequences of these in terms of reduced investment and limited social benefit from the technology. These shortcomings are as follows:

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[21] Advisory Committee on Releases into the Environment. 2013 *Report 1: Towards an evidence-based regulatory system for GMOs*. UK Gov (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/239839/an-evidence-based-regulatory-system-for-gmos.pdf (accessed 3 May 2023).

Assumption that use of the GM method creates unpredictable risks

The EU's approach to regulating GM crops is based on the prevailing uncertainty that existed in the 1990s, when use of the GM method for crop improvement was not established and feared by some to be inherently harmful. At the time, every new GM crop was regarded as having the potential to present new risks to human health and the environment. This has resulted in the process-based, rather than outcome-based, approach to regulation, which required extensive risk assessment of every organism created using the GM method[22], irrespective of its specific properties.

Widespread global use of recombinant DNA technologies in the intervening 30 years has resolved the uncertainty about whether there is something inherently risky about using the method. An extensive analysis conducted by the US National Academies of Sciences, Engineering and Medicine found that GM crops and food present no greater risk to human health and the environment than non-GM crops and food[23]. This is implicitly acknowledged in reforms made in 2022 to the Department for the Environment, Food and Rural Affairs' rules governing field trials of plants carrying GM traits which allow use of the GM method to create 'Qualifying Higher Plants' so long as that plant "could have occurred naturally"[24].

Furthermore, genomics analysis of crops has shown that the genetic variation between varieties of the same species[25] vastly exceeds any variation that researchers and breeders can introduce either by gene editing or the GM method. Such research has also revealed the historic horizontal gene transfers discussed in Chapter 1 that means species such as sweet potato are naturally transgenic.

Rather than resulting from use of the GM method *per se*, any potential for harm is determined by the biochemical or environmental effects of the specific genetic change introduced, such as producing a new protein or changing the parts of a plant a protein is produced in, rather than resulting from use of the GM method. Whilst it is reasonable to assess new GM events for specific risks linked to the trait that has been introduced, the requirement for all GM crops to be assessed for non-specific risks is not justified by the accumulated evidence about the consequences of using the GM method. This barrier is compounded by the second shortcoming, which is how the risk assessment requirements have been implemented.

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[22] Kok E J, Glandorf D C M, Prins T W and Visser R G F. 2019 *Food and environmental safety assessment of new plant varieties after the European Court decision: Process-triggered or product-based?* Trends in Food Science & Technology 88:24-32. doi: 10.1016/j.tifs.2019.03.007.

[23] National Academies of Sciences, Engineering, and Medicine. 2016 *Genetically Engineered Crops: Experiences and Prospects*. Washington, DC: The National Academies Press.

[24] The Genetically Modified Organisms (Deliberate Release) (Amendment) (England) Regulations. 2022 https://www.legislation.gov.uk/uksi/2022/347/made/data.xht].

[25] McCouch S R and Rieseberg L H. 2023. Harnessing crop diversity. Proceedings of the National Academy of Sciences of the United States of America, 120(14), e2221410120. https://doi.org/10.1073/pnas.2221410120

Risk assessments are formulaic rather than case-by-case

Although the EU regulatory framework for GM crop risk assessment allows for developers to make the case that some risk assessment requirements are not relevant to the potential risks of their specific trait in a particular specific crop, in practice EU regulators have asked for evidence about potential harms for which there is no plausible mechanism. The consequence of this is what ACRE describes as "open-ended data gathering exercises" (p. 1 – 2) in which "data are requested and included in ERAs [Environmental Risk Assessments] that do not inform decisions on risk. This is confusing and adds to the regulatory burden without improving environmental protection" (p. 9)[26].

Whenever a regulatory agency asks for further information from a crop developer as part of the risk assessment process, this adds to the time and expense associated with developing that crop and delays the realisation of any societal benefits from its cultivation. ACRE cites evidence that the average time between submission and approval for conventionally bred crops is two and half years, whereas over half of the 18 applications to cultivate GM crops in the EU regulatory pipeline at the time they wrote their report in 2013 had been there for more than five years. No new GM crop has been approved for cultivation and grown in the European market since Bt maize in the 1990s, which has been continuously grown in Spain since 1998 and comprised roughly 30% by area of Spain's maize production between 2013 – 2021[27].

ACRE also highlighted that the administration and testing fees for conventionally bred varieties were £5000, compared with £5 – 10 million for GM crop varieties.

With regard to the General Surveillance requirements for Post Market Environmental Monitoring, ACRE highlights the impracticality of ongoing monitoring for a non-specific threat and the difficulty of relating the cause of any actual impacts to an individual plant variety or any GM trait it might carry.

2.4 Consequences of disproportionate implementation

The way the EU has applied the GM regulatory framework has prevented deployment of a useful method to reduce the environmental impact of agriculture and to improve the quality of the human diet. The time-consuming, expensive and unpredictable regulatory process applied by the EU means that only multinational companies have the resources to develop GM crops. The high regulatory hurdle is one explanation for the fact that many of the historic uses of GM have been to make crops that are compatible with synthetic inputs, particularly herbicides, that these same companies make. Delayed approvals have also added to the opportunity cost of continuing to use chemistry rather than genetics to control agricultural pests and diseases. For example, the longer a late blight resistant potato variety is delayed, the longer farmers will choose to control the disease by 15 – 20 agrichemical applications per season. This illustrates the importance of making judgements in a manner that includes balancing the cost of not using the method against any hypothetical costs of using it.

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[26] Advisory Committee on Releases into the Environment. 2013 *Report 1: Towards an evidence-based regulatory system for GMOs*. UK Gov (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/239839/an-evidence-based-regulatory-system-for-gmos.pdf (accessed 3 May 2023).

[27] Areal F J and Riesgo L. 2022. *Sustainability of Bt maize in Spain (1998 – 2021): an economic, social and environmental analysis*. Fundacion-Antama (online). Available at: https://fundacion-antama.org/wp-content/uploads/2022/04/20220418-INFORME-BENEFICIOS-1998-2021-english_FINAL_.pdf (accessed 9 May 2023).

Outside of the EU, the UK can take an approach to regulation of crops improved with the GM method that is proportionate to the risks of specific traits in individual organisms. This would increase the feasibility for start-up companies and university spin-outs to commercialise the GM traits and crops with the kind of agronomic, environmental, and consumer benefits necessary to address current agricultural challenges.

Section recap

This section showed that all crop varieties are rigorously tested for any agricultural defects before they can be sold to farmers. GM crops face additional tests for risks to human health and the environment, and the way this risk assessment is applied by the EU is no longer in proportion to the likelihood that any changes that are introduced are a risk to either human health or the environment. This approach to regulation has made it more difficult to use the technology to realise societal benefits. The next section presents proposals for a more enabling implementation of the current regulations.

More proportionate application of the current framework

The previous section described the inflexible and burdensome way in which EU regulators chose to implement the GMO regulatory framework. As part of the process of leaving the EU, the UK transposed the same framework into UK law. However, the wording of this framework provides applicants with the opportunity to seek a derogation from requirements that are not relevant to their product. In other words, there is the flexibility to only submit evidence to address specific risk hypotheses on a case-by-case basis.

One component of the current framework that has been singled out for providing little scientific benefit is the 90-day rodent feeding trial[28]. Studies performed on behalf of the European Commission have shown that these trials are of little scientific benefit in terms of assessment of non-specific risks[29] and they are inconsistent with wider policy objectives of minimising the use of animals in research[30]. Rodent feeding trials are not the only requirement that has been criticised for not being related to a specific or credible risk hypothesis, with another one being the requirement for extra risk assessments in all cases where multiple genes have been included in the same crop (referred to as 'stacked events') even if the risks of the genes have been previously assessed when introduced individually[31].

A separate issue that adds to the burden of GM crop development is the requirement for GM approvals to be renewed every 10 years even though there are mechanisms to revoke the approval of a GM crop if there is evidence of unanticipated harms. The Government should therefore review both the content and implementation of all of the GM regulatory requirements that have been transposed into UK law and consider how to manage or adjust those that add no value to the risk assessment process or are effectively managed through other parts of the crop regulatory system such as the VCU and DUS evaluations.

When considering applications from GM crop developers, the data required by UK regulators should take into account crop type, nature of the modification, scale of the release and experience of regulating and deploying the GM trait in other parts of the world. Presented below are some ideas for how to apply the GM regulations in a manner that is proportionate to the potential risks of individual varieties with GM traits and consistent with the interpretation of the precautionary principle set out by ACRE[32]. As these suggestions relate to how existing regulations are applied, this approach could be adopted immediately without any further legislative reform.

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[28] Rodent feeding trials require rodents to be fed with any GMO intended for human food or animal feed for 90 days.

[29] G-TWYST, GRACE. 2018 Policy Brief: Animal feeding studies for GMO risk assessment. Lessons from two large EU research projects. https://www.julius-kuehn.de/media/Presse/2018/PDF/PI2018_G-TwYST_and_GRACE_Policy_Brief.pdf

[30] Devos Y, Naegeli H, Perry J N and Waigmann E. 2016. 90-day rodent feeding studies on whole GM food/feed: Is the mandatory EU requirement for 90-day rodent feeding studies on whole GM food/feed fit for purpose and consistent with animal welfare ethics?. EMBO reports, 17(7), 942–945. https://doi.org/10.15252/embr.201642739

[31] Advisory Committee On Releases To The Environment. 2013 Report 3: Towards a more effective approach to environmental risk assessment of GM crops under current EU legislation. UK Gov (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/239893/more-effective-approach-gmo-regulation.pdf (accessed 26 September 2023)

[32] A 2002 ACRE paper on assessing the harms of genetically modified organisms states: "The precautionary principle is used in decision making about releases. The principle states that if a preliminary scientific assessment shows there are reasonable grounds for concern that potentially dangerous effects will occur on valued and protected aspects of the environment, human, animal or plant health then a release will not proceed until sufficient knowledge has been gained to be able to make a decision based on risk assessment".

The proposals are aligned with the goals set out in the Government's 2023 "Smarter Regulation" policy, which recognises that "some of the current regulatory standards inherited from the EU are based on an overly restrictive and often disproportionate interpretation of the precautionary principle"[33]. They are also aligned with the Government's Science and Technology Framework that regulation should be "pro-innovation, stimulates demand for science and technology and attracts investment while representing UK values and safeguarding citizens"[34]. They build on the recommendations of the Government's own advisory group, the Regulatory Horizons Council, which produced a report for the Department of Business, Energy and Industrial Strategy in 2021 (updated in 2022) on the regulation of genetic technologies[35].

The proposed approach is based on two questions:

1. Has the crop that has been modified, the trait that has been introduced, and/or the Mechanism of Action (the biochemical processes through which genetic material determines a trait) previously been assessed in relevant environments?
2. Is there a plausible causal mechanism by which the GM crop could lead to harm?

3.1 Using previous regulatory experience to inform assessment

Decisions on whether extensive new risk assessment is required should be based on prior experience with the species into which the trait has been introduced, the nature of the trait eg drought tolerance or disease resistance, the 'Mechanism of Action', the intended use, and the receiving environment. If previous regulatory experience in other countries has found no evidence of risk in comparable environments and for comparable uses, then applicants should be able to use this as part of the dossier they compile to justify a derogation from UK regulatory requirements. This would be consistent with the approach that will be taken in the context of medicines and medical technologies where, from 2024, the UK will adopt "near automatic sign-off for medicines and technologies already approved by trusted regulators in other parts of the world such as the United States, Europe or Japan"[36]. In the context of GM, this approach to regulation works exactly for the health risks assessed by the FSA and ACRE, but environmental risks are more dependent on the context so any differences between the receiving environments would need to be assessed before lack of a plausible mechanism of harm in another country could be used to justify a derogation in the UK.

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[33] Department for Business and Trade. 2023 Smarter Regulation to Grow the Economy. UK Gov (online). Available at: https://www.gov.uk/government/publications/smarter-regulation-to-grow-the-economy/smarter-regulation-to-grow-the-economy (accessed 19 October 2023).

[34] Department for Science, Innovation and Technology. 2023 *UK Science and Technology Framework*. (p.16) (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1140217/uk-science-technology-framework.pdf (accessed 26 July 2023).

[35] Regulatory Horizons Council. 2022 *Reforming the Governance of Genetic Technologies: Policy Brief by the Regulatory Horizons Council*. UK Gov (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1087567/regulatory_horizons_council_policy_brief_on_genetic_technologies.pdf (accessed 12 July 2023).

[36] HM Treasury Spring Budget 2023 speech. UK Gov (online). Available at: https://www.gov.uk/government/speeches/spring-budget-2023-speech (accessed 19 October 2023).

If previous regulatory experience has identified a risk then applicants should provide evidence that they have managed that risk in their product.

3.2 Restrict data requirements to risks with a plausible causal mechanism

Where there is no previous regulatory experience with the specific combination of crop, trait and mechanism of action, then ACRE should only ask for data for risk assessment where there is a plausible causal mechanism – ie a defined and scientifically credible hypothesis for how adverse effects might arise from the GM crop and potential for these adverse effects to occur under field conditions. This would avoid the 'open-ended data gathering' exercises criticised by ACRE. The risks to be assessed in all new GM plant varieties would remain the same as those set out for GMOs in EU Directive 2001/18/EC[37].

In working out whether a GM crop presents a plausible risk and what is proportionate in terms of regulation, it is important that GM crop developers and regulators work together. Detailed evidence should only be required where there is a plausible mechanism for how the characteristics of the new variety might lead to harm. Assessing plausibility will depend on both the regulators' and businesses' experience and expertise.

To implement this, the Regulatory Horizons Council recommended GM crop developers and regulators engage in discussions about the expected regulatory requirements at an early stage of the development process, and this report endorses that recommendation. As with preliminary opinions provided by ACRE under the current framework, these early stage discussions between developers and regulators should be published.

The recommendation that detailed evidence should only be required for harms with a plausible causal mechanism is based on the approach established by the United States Department of Agriculture's *Regulatory Status Review* process[38] for assessing whether there is a plausible pathway by which the modified plant could cause an environmental harm (defined in the USDA framework as 'plant pest risk'). Annex B provides further detail from the guidance provided by the US regulator on how they assess whether there is a scientifically plausible pathway for a GM crop to cause an environmental harm.

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[37] The risks set out in EU Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms are:
- disease to humans including potential allergenic or toxic effects;
- disease to animals and plants including toxic, and where appropriate, allergenic effects;
- effects on the dynamics of populations of species in the receiving environment, including the potential of the crop to become a weed (its potential for invasiveness and persistence), and the genetic diversity of each of these populations;
- altered susceptibility to pathogens facilitating the dissemination of infectious diseases and/or creating new reservoirs or vectors and/or driving the evolution of pathogens so they become more virulent or better able to expand the range of species they can infect;
- compromising prophylactic or therapeutic medical, veterinary, or plant protection treatments, for example by transfer of genes conferring resistance to antibiotics used in human or veterinary medicine; and
- effects on biogeochemistry (biogeochemical cycles), particularly carbon and nitrogen recycling through changes in soil decomposition of organic material.

[38] Animal and Plant Health Inspection Service. 2022 *Guide for Requesting a Regulatory Status Review under 7 CFR part 340*. United States Department of Agriculture (online). Available at: https://www.aphis.usda.gov/brs/pdf/rsr-guidance.pdf (accessed 26 April 2023).

Image
GM purple tomatoes on sale at a market in North Carolina, USA.

Under the USDA process, if there is no plausible mechanism by which the modified plant presents an increased environmental risk then the developer does not have to invest in studies investigating it. This significantly reduces the regulatory cost of developing a GM crop with traits that are highly unlikely to pose an increased environmental risk. Another important component of this process for reducing the regulatory burden is a commitment to making decisions within 180 days. This reasonable time frame for decisions on deregulation enables faster iteration in response to feedback from regulators. This reduces total development time and total development cost, which is particularly important for small enterprises.

The first GM plant to be approved under this framework in the US was the anthocyanin-rich tomato developed by scientists at the John Innes Centre in Norwich (further details of this are included in Annex A). The US regulator concluded that, based on their experience of tomato varieties, the traits that alter fruit colour and nutritional quality, and the modifications made in the GM tomato, there was no reason to believe that it posed an increased plant-pest risk compared with other commercially grown tomatoes and therefore was exempt from the USDA GM crop regulatory framework[39].

The USDA *Regulatory Status Review* process only applies to the potential for a GM plant to present an increased risk to crops or other organisms used in agriculture. GM crop developers are expected by retailers to satisfy the US Food and Drug Administration before they will sell GM plant products for human consumption. GM crops with resistance traits against diseases or pests also need approval from the US Environmental Protection Agency. These distinct roles are a function of the regulatory framework in the US and there is no reason the UK should not apply the principle of using prior regulatory experience to all aspects of GM risk assessment.

As ACRE's remit includes environmental risks, given the known environmental impacts of many current agricultural practices, ACRE could take into account whether the overall impact of cultivating the GM crop will be to reduce environmental harm compared with the *status quo*.

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[39] Animal and Plant Health Inspection Service. 2022 *APHIS Issues First Regulatory Status Review Response: Norfolk Plant Sciences' Purple Tomato*. United States Department of Agriculture (online). Available at: https://www.aphis.usda.gov/aphis/newsroom/stakeholder-info/sa_by_date/sa-2022/purple-tomato (accessed 27 April 2023).

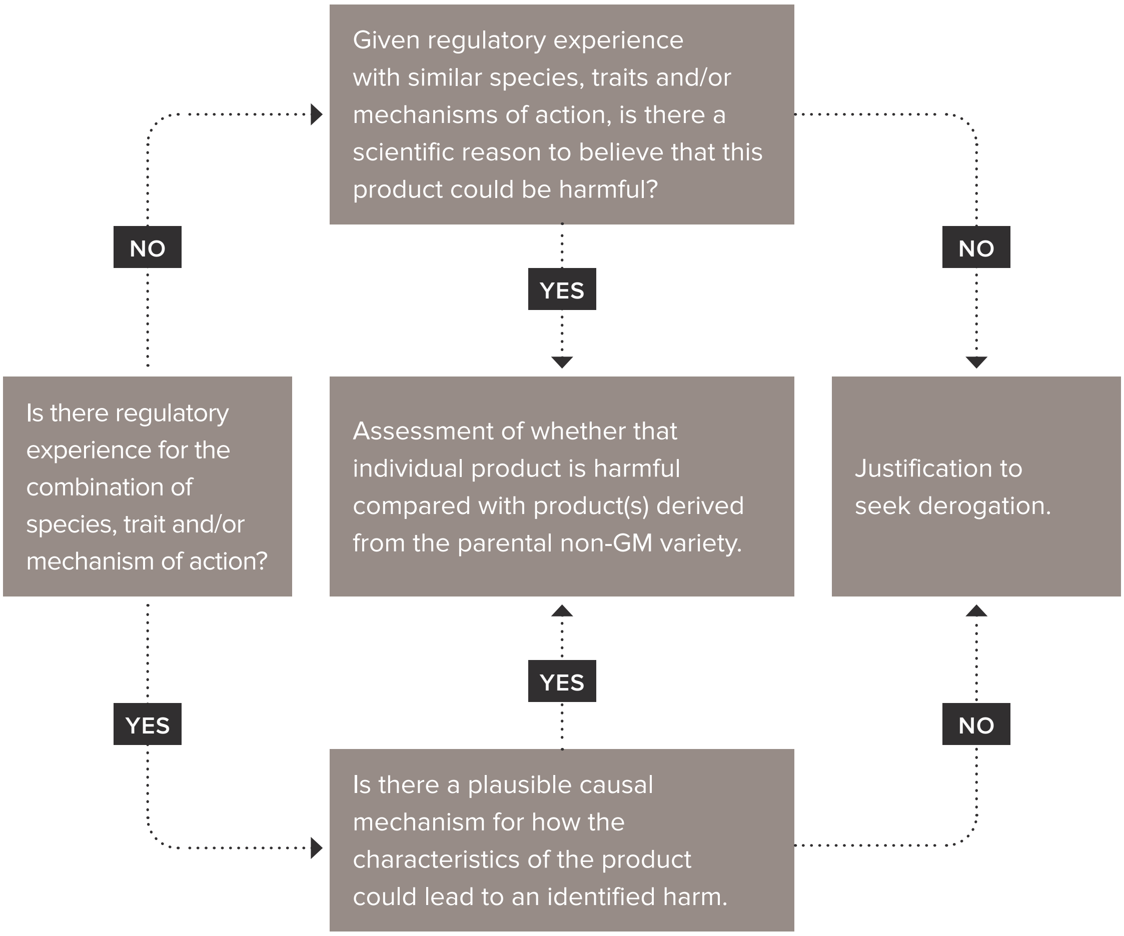
3.3 Illustrative examples of how the proposed approach would work

To help understand how the proposed approach could work in practice, below is a flow diagram and worked examples based on some of the applications of the GM method discussed in greater detail in Annex A.

FIGURE 1

How prior experience can inform decisions on risk assessment requirements.

Flow diagram to illustrate what can reasonably expected of a developer to justify an application for derogation to a regulator. ‘Product’ as used in this figure follows the definition set out in Regulation (EC) No 1829/2003 of “a GMO to be used as a source material for production of food or feed and products for food and/or feed use which contain, consist of or are produced from it, or to foods or feed produced from a GMO”[40]. “Harmful” follows the risks identified in EU Directive 2001/18/EC[37].



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[40] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (online). Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2003R1829:20080410:EN:PDF (accessed 19 October 2023).

3.3.1 Assessing potential risk to human health in late blight resistant potatoes

Potatoes are known to contain glycoalkaloids which can be toxic to humans if consumed in high amounts. Glycoalkaloids occur in different parts of a potato plant, with the highest levels in leaves, flowers, and sprouts and the lowest in the tubers. Commercial potato cultivars typically have a total glycoalkaloid content in the tubers between 10 and 150 mg/kg fresh weight. Tissue culture and the GM method could conceivably change the biological mechanisms that regulate glycoalkaloid content in the tubers, and elevated glycoalkaloids could lead to a risk to human health. The regulator would therefore be justified in asking a GM potato developer for evidence that their product did not have elevated levels of glycoalkaloids in the tubers. It should be noted that the same risk applies to conventionally bred potatoes and non-GM potato breeders routinely test for glycoalkaloid levels in new varieties.

As regards the trait and mechanism of action, blight resistance is a trait that has been selected for in conventionally-bred potatoes without any demonstrable risk to human health or the environment and so should not require any specific investigation in GM potatoes. Similarly, the mechanism of action based on intracellular immune receptors is one that is common to many crop varieties so would not justify new investigations.

3.3.2 Assessing potential risk of crops with enhanced photosynthesis from chloroplast-localised cyanobacterial flavodoxin

Blue-green algae, such as spirulina, produce a protein called flavodoxin as part of their photosynthetic machinery. Terrestrial plants use an iron-containing alternative protein, ferredoxin, that plays the same role in their photosynthesis. Introducing the gene that encodes flavodoxin into terrestrial plants has been shown to increase tolerance to drought, chilling, oxidants, heat and iron starvation[41]. This might be a useful phenotype in any crops subject to high light and water stress.

As there has been no previous commercial use of the GM method to express flavodoxin protein in crop plants, there is no direct regulatory experience of the trait and mechanism of action. Regulators should therefore ask whether there is a plausible causal mechanism by which this protein could cause harm. As spirulina has a history of human consumption in central America and is widely consumed as a dietary supplement without evidence of harm, this suggests there is not a plausible risk to human health from consuming blue-green algae-derived flavodoxin.

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[41] Zurbriggen M D, Tognetti V B, Fillat M F, Hajirezaei M R, Valle E M and Carrillo N. 2008. *Combating stress with flavodoxin: a promising route for crop improvement*. Trends in biotechnology, 26(10), 531–537. https://doi.org/10.1016/j.tibtech.2008.07.001

It would therefore be reasonable to ask developers to compare the specific flavodoxin incorporated into the GM crop to the corresponding gene from spirulina. Assuming no significant differences at the genetic level, regulators could also ask developers to demonstrate that the concentration of flavodoxin within the part of the plant that is used for food or feed is within the same range as found in spirulina.

With regard to environmental harm, there is a plausible risk that the trait of enhanced tolerance to abiotic stress could cross to wild relatives of the crop. Regulators would therefore expect the developer to have assessed the potential for increased weediness if wild relatives cross with the crop plant and acquire the stress tolerance conferred by the flavodoxin gene.

3.3.3 Assessing consequences of producing elevated levels of omega-3 long-chain polyunsaturated fatty acids in *Camelina sativa*

Camelina sativa is a plant in the Brassicaceae family grown as a source of vegetable oil. Scientists have introduced genes from marine algae into *Camelina sativa* that encode enzymes that make long chain omega-3 fatty acids. These algae-derived omega-3 fatty acids can be extracted from the seeds of *Camelina* plants with the GM trait and used in place of omega-3 oils derived from wild-caught fish for human consumption and aquaculture.

Although there is no specific regulatory experience of this trait in this species, experience from the cultivation of oil-bearing seeds and human and animal consumption of omega-3 oils indicates there is no plausible mechanism by which this crop species with this GM trait could pose an increased environmental or health risk compared with *Camelina sativa* without the GM trait. This means no environmental risk assessment would be required for authorisation for cultivation. With regard to authorisation for food and feed, the Food Standards Agency could ask for evidence that the resulting oil composition lies within the range of commercial fish oil supplements available on the market. If the oil composition is within the range of other products already on the market, the issue of whether the material is sourced from a GM crop becomes irrelevant, as no proteins or nucleic acids will be present in the oil product. The meal remaining after pressing the oil might be used for animal feed in which case the levels of the algae-derived proteins that are present in this meal should be measured and reported by the developer.

The general principle should be that if a product sourced from a GM crop is indistinguishable from that produced from a non-GM crop, then whether or not the source crop is GM becomes irrelevant. A similar argument would apply to sugar (sucrose) from sugar beet, which is indistinguishable irrespective of whether it is derived from a GM sugar beet or a non-GM sugar beet.

3.4 Proportionate implementation of Post-Market Environmental Monitoring

As discussed in Section 2.2, the legislation transposed into UK law requires ‘general surveillance’ of GM crops to monitor for any unforeseen risks. In a 2013 report, the Advisory Council on Releases to the Environment set out proposals for how this function could be fulfilled in a proportionate manner[42]. The goal of this approach is to make the most of the scope within the regulations to use existing environmental surveillance networks to avoid duplication in the surveillance of different GM crops and adding to the expense of GM regulation. This approach would enable identification of environmental changes that might be connected to the cultivation of GM crops. Should adverse effects be identified, then expert opinion would be needed by ACRE to determine the likelihood of the change being connected to the GM crop and therefore what further action is needed to determine the cause.

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[42] Advisory Council on Releases to the Environment. 2013 *Post Market Environmental Monitoring of Genetically Modified Crops* (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/239164/acre_pmem_of_GMOs.pdf (accessed 16 August 2023).

What might a future regulatory system look like?

The discussion so far has focused on how changes to the implementation of the current regulatory framework for GM crops could ensure that the information requested from GM crop developers is more proportionate to the risks of what they have produced. However, it still follows a 'rules-based' approach to regulation that assumes risk is determined by the technology used to make a genetic change. As discussed above, 30 years of regulatory experience with the GM method in plants has shown that there is no evidence of a greater risk to human or animal health, or the environment, from production or consumption of GM food and feed compared with non-GM equivalents[43]. As a 2018 report for the UK Government on the advantages and disadvantages of goals-based and rules-based approaches to regulation notes, a known limitation of rules-based approaches is that they are overly inflexible and prescriptive[44]. This has proved to be the case with GM regulation given the uncertainty about how to regulate gene editing products and the disproportionate approach taken by the EU.

An alternative to the rules-based regulatory paradigm is goals- or outcomes- based[45] regulation. Outcomes-based approaches have been increasingly adopted both internationally and in the UK (particularly in the context of Health and Safety regulation). Such approaches have the advantage of being more conducive to innovation by ensuring that products with similar risks face the same regulatory requirements. The Regulatory Horizons Council has developed proposals for how such an outcomes-based approach could work for the regulation of genetic technologies used in agriculture[46]. This would include prospective but less imminent engineering and synthetic biology driven innovations.

Under the Regulatory Horizons Council's proposals, the products of current breeding technologies that are not regulated as GM crops would remain outside this proposed outcomes-based regulatory framework. To some extent this maintains a process-based trigger but the effects of this would be mitigated by what they refer to as a "guiding assumption" that "similar products (phenotypically and genetically) arising from different genetic techniques would not be expected to have different risks and so should be subject to similar regulatory scrutiny".

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[43] National Academies of Sciences, Engineering, and Medicine. 2016 *Genetically Engineered Crops: Experiences and Prospects*. Washington, DC: The National Academies Press.

[44] Decker C. 2018 *Goals-based and rules-based approaches to regulation – BEIS Research Paper Number 8*. Department for Business, Energy and Industrial Strategy (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/714185/regulation-goals-rules-based-approaches.pdf (accessed 31 July 2023).

[45] *Ibid*

[46] Regulatory Horizons Council. 2022 *Reforming the Governance of Genetic Technologies: Policy Brief by the Regulatory Horizons Council*. UK Gov (online). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1087567/regulatory_horizons_council_policy_brief_on_genetic_technologies.pdf (accessed 12 July 2023).

This implies that where any genetic technology has been used to create a product that is similar to a conventional breeding product, it should face the same regulatory scrutiny as conventionally bred products. The approach would be based on similar principles to those set out in Chapter 3 of this report that prior experience should inform whether extensive risk assessment is required. This would limit the requirement for extensive new studies for highly innovative products which regulators had no prior experience of.

Adopting the Regulatory Horizons Council's proposed approach would have the advantage that it is flexible enough to keep pace with technological developments whilst enabling regulators to apply their expertise to balancing risks and benefits of genetic technologies to achieve societal goals.

A further aspect of the Regulatory Horizons Council's proposals is a Stakeholder Advisory Panel that would inform regulatory decisions. This relates to the discussion in Chapter 1 that social licence for GM crops is influenced by the purpose for which the crop has been modified. Whilst the panel would not comment on individual product assessments, it would provide a forum for societal advice and feedback on the kinds of outcomes that would be acceptable and whether the risks of not using a GM crop outweigh the risks of using it.

Conclusion

This report argues that the GM method complements the long history of breeding crop plants from their wild ancestors and of recruiting useful genetic variation into crop plants from their wild relatives. The examples discussed show that the GM method enables unique opportunities to achieve plant breeding outcomes that promote the goals of resilient supply of nutritious food whilst minimising environmental impacts. Whether this opportunity is realised will depend in part on the risk assessment requirements for GM crops. If the UK continues to implement the regulations for GM crops as does the EU, this will continue to limit the opportunity to translate publicly funded research into socially useful outcomes.

Instead, the UK should learn from the regulatory experience of countries that have made greater use of the technology and implement the current regulatory framework in a way that takes a case-by-case approach to risk assessment based on the scientifically plausible risks of a new GM trait. In the longer term, the UK could follow the emergent trend of outcomes- rather than rules-based approaches to regulation. This approach would focus on the outcome achieved rather than the breeding technology used to ensure regulation keeps pace with developments in both breeding technologies and understanding of the risks associated with using those technologies.

Proportionate implementation of the current framework in the short term and carrying out more fundamental reforms in the longer term will help capitalise on UK plant science and plant breeding expertise to deliver the innovation that is needed both in the UK and internationally to deal with the immense challenges facing sustainable food production.

ANNEX A

Useful implementations of the GM method

This annex provides further detail on the examples discussed in section 1.3 to demonstrate the potential societal benefits of more extensive deployment of crops improved with GM traits.

The list is not exhaustive and reflects in part the expertise of one co-author (Professor Jonathan Jones FRS) in the field of plant immunity. Many of the patents that previously restricted use of GM methods (including selectable marker genes, as discussed below) have now expired so most of these technologies could be deployed readily, though for any particular trait, intellectual property considerations may require a licence to that specific technology. We do not discuss implementations in tree crops (though several exist) since their deployment is likely to take longer.

To use the GM method, a selectable marker gene is usually required. The bacterial neomycin phosphotransferase 2 (NPT II) gene is commonly used to select plant cells that have received the gene(s) of interest; NPT II has long been recognised as posing no risk to human health[47].

As an alternative, herbicide resistance can be used. Some herbicides work by inhibiting plant (but not animal) enzymes; for example, sulfonylureas such as chlorsulfuron inhibit an enzyme (acetolactate synthase, ALS) required for branched chain amino acid synthesis, thus starving the plant of these essential amino acids. Forms of ALS exist that resist inhibition and that can therefore be used as selectable marker genes. If derived from the recipient species, a herbicide resistant ALS could enable cisgenic status (ie all genes delivered using the GM method are potentially crossable with the crop), but a GM crop produced using the bacterial NPT II gene could never be granted cisgenic status.

Resistance to pests and diseases

Fungi, viruses, bacteria and oomycetes cause many crop diseases, such as wheat rusts or potato late blight[48]. The United Nation's Food and Agriculture Organisation estimates that over US$220 billion worth of damage is caused by plant pathogens every year and a further US$70 billion by invasive pests[49]. Climate change is expected to increase the risk to cereal and horticultural crops by enabling pests and diseases to establish themselves in new areas[50].

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[47] US Food and Drug Administration. 1994 21 CFR Parts 173 and 573. (online). Available at: https://www.govinfo.gov/content/pkg/FR-1994-05-23/html/94-12492.htm (accessed 6 September 2023).

[48] Wang Y, Pruitt R N, Nürnburger T and Wang Y. 2020 *Evasion of plant immunity by microbial pathogens.* Nature 20:449-464. doi:10.1038/s41579-022-00710-3.

[49] Food and Agriculture Organization of the United Nations (FAO). 2021 *Climate change fans spread of pests and threatens plants and crops, new FAO study* (online). Available at: https://www.fao.org/news/story/en/item/1402920/icode/ (accessed 16 June 2023).

[50] IPPC Secretariat. 2021 *Scientific review of the impact of climate change on plant pests – A global challenge to prevent and mitigate plant pest risks in agriculture, forestry and ecosystems*. FAO on behalf of the IPPC Secretariat (online). Available at: https://www.fao.org/3/cb4769en/online/src/html/copyright.html (accessed 11 July 2023).

As well as the economic cost, interventions to prevent pests and diseases have an environmental cost. One of the major challenges for sustainable agriculture in high income countries is to reduce the use of synthetic inputs such as pesticides without reducing yields. Synthetic inputs are costly and can cause environmental damage. The production and application of these inputs inevitably results in greenhouse gas emissions, soil compaction, negative impacts on non-target organisms and disruption of the soil microbiome. Their cost and availability are particular challenges for farmers in low-income countries who need to increase yields but often cannot afford or access the inputs.

Previous GM crops that have reduced dependence on synthetic inputs have been criticised for benefitting producers without benefitting consumers[51]. But such arguments ignore the fact that reducing the use of these inputs and their associated environmental impacts is a public benefit.

Immune receptors, often encoded by resistance genes

Plants have powerful defence responses against pathogens, but to be effective, these defences must be promptly activated upon pathogen arrival. This requires detection of pathogen-derived molecules by immune receptors located either at the cell surface or inside the plant cell. Most plant Resistance (*R*) genes encode intracellular immune receptors. Although plants usually carry 100s to 1000s of immune receptor genes, an individual plant or crop variety can only detect a subset of pathogen-derived molecules and crop plants often lack detection capacities that are present in wild relatives or other plants. Genes encoding immune receptors with such detection capacities can be identified in these plants and brought into the crop using the GM method.

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[51] Friends of the Earth International. 2014 *Who benefits from gm crops? An industry built on myths* (online). Available at: https://www.foeeurope.org/sites/default/files/publications/foei_who_benefits_from_gm_crops_2014.pdf (accessed 22 July 2023).

Late blight resistant potatoes

Scientists at The Sainsbury Laboratory (TSL) in Norwich have used this approach to develop a genetically modified variant of the UK's most widely grown potato variety, Maris Piper, that is resistant to late blight. Late blight is the most significant potato disease in the UK, costing around £50 million per year in crop losses and synthetic inputs[52]. Farmers usually spray their crops about fifteen times a season with fungicides to prevent late blight, which contributes to climate change through the emissions associated with their manufacture and application, damages soil microbiota[53] and also soil structure from tractor journeys, and perhaps most significantly, selects for resistance to the compounds used to treat fungal disease in humans[54]. A particular challenge for farmers is that blight is more severe under cool, wet weather conditions that often lead to water-logged soils that hinder fungicide applications in the very conditions most conducive to disease.

To reduce the dependence on fungicides, scientists introduced genes from two wild relatives of the potato (domesticated potato is *Solanum tuberosum* and the genes came from other *Solanum* species). The addition of three immune receptor genes greatly reduces the risk of emergence of resistance-breaking blight races. A similar approach has been used to develop blight-resistant potatoes for African potato farmers[55]. Potatoes using immune receptors from wild relatives discovered at TSL and introduced using the GM method are already being grown in the USA.

Stem rust resistant wheat

Wheat is the third largest staple crop, providing roughly 20% of dietary calories and protein worldwide[56]. Wheat stem rust is a major disease of this crop, causing losses of up to 6.2 million tonnes (worth an estimated $1.12 billion) annually. The last severe stem rust epidemic in England occurred in 1955 and caused average yield losses of 50%.

Thanks to resistant varieties developed through conventional plant breeding, the disease has been largely absent in western Europe since then. However, in 1998 a new strain of stem rust emerged that could infect previously resistant varieties, which led to outbreaks in Germany in 2013 and Sicily in 2016. An analysis in 2019 of UK wheat varieties found that more than 80% of the 57 varieties tested were highly susceptible to

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[52] Garry F K, Bernie D J, Davie J C S, Pope E C D. 2021 *Future climate risk to UK agriculture from compound events*. Climate Risk Management 32, no. 8: 100282. https://doi.org/10.1016/j.crm.2021.100282doi:10.1016/j.crim.2021.100282.

[53] Edlinger A, Garland G, Hartman K, Banerjee S, Degrune F, Garcia-Palacios P, Hallin S, Valzano-Hld A, Herzog H, Jansa J, Kost E, Maestre F T, Pesador D S, Philippot L, Rillig M C, Romdhane S, Saghai A, Spor A, Frossard E and Heijden M G A. 2022 *Agricultural management and pesticide use reduce the functioning of beneficial plant symbionts.* Nature Ecology & Evolution 6 :61145–1154. doi:10.1038/s41559-022-01799-8.

[54] Fisher M C, Alastruey-Izquierdo A, Berman J, Bicanic T, Bignell E M, Bowyer P, Bromley M, Brüggemann R, Garber G, Cornely O A, Gurr S J, Harrison T S, Kuijper E, Rhodes J, Sheppard D C, Warris A, White P L, Xu J, Zwaan B, and Verweij P E. 2022 *Tackling the emerging threat of antifungal resistance to human health*. Nature reviews Microbiology 20, no. 9:557-571. doi:10.1038/s41579-022-00720-1.

[55] Ghislain M, Byarugaba A A, Magembe E, Njoroge A, Rivera C, Roman M L, Tovar J C, Gamboa S, Forbes G A, Kreuze J F, Barakye A and Kiggundu A. 2019 *Stacking three late blight resistance genes from wild species directly into African highland potato varieties confers complete field resistance to local blight races*. Plant Biotechnol. J 17, no. 6: 1119-1129. doi: 10.1111/pbi.13042.

[56] Shiferaw B, Smale M, Braun H J *et al*. 2013 Crops that feed the world 10. Past successes and future challenges to the role played by wheat in global food security. Food Sec. 5, 291–317. https://doi.org/10.1007/s12571-013-0263-y

infection by the strain of stem rust prevalent in the 2013 outbreak in Germany[57]. Despite the previous success of conventional breeding programmes to develop wheat varieties that are resistant to stem rust, the emergence of more virulent strains of the fungus highlights the constant evolutionary battle between diseases and their hosts.

Introducing more than one resistance gene makes it harder for pathogens to overcome genetic disease resistance, but this is very time consuming and expensive using conventional breeding.

In 2021 an international group of researchers demonstrated that introducing five resistance genes using the GM method made a GM wheat that is highly resistant to stem rusts, including strains that infect all conventionally-bred resistant varieties of wheat[58]. Whilst this approach cannot guarantee this form of resistance will never be overcome, it is likely to be more durable than conventional approaches and significantly reduces the time required to develop new resistant varieties. A similar approach could control the other main wheat rust diseases, stripe rust and leaf rust.

Virus resistance in multiple species

Plant viruses also reduce crop yields and *R* genes against them often encode an immune receptor that can recognise multiple related viruses. For example, the potato resistance gene $\mathrm{Ry}_{\mathrm{sto}}$ recognises the coat protein not only of Potato Virus Y, but also many related potyviruses such as plumpox virus and turnip mosaic virus[59]. Thus, a potato virus resistance gene, if transferred to the appropriate species, could confer resistance to many other viruses. Similarly, the Rl_{adg} gene of potato[60] that confers resistance to the potato leaf roll virus could confer resistance to many other poleroviruses such as beet mild yellowing virus and beet western yellows virus that cause yellowing and yield loss in sugarbeet and also turnip yellows virus that causes yield losses in Brassicaceae. Recently, tomato brown rugose virus has emerged and is causing major challenges for tomato production worldwide[61]. Resistance genes found in tobacco protect against this virus[62], and introducing them into tomato with the GM method should provide a general and durable solution for its control.

Resistance to bacterial diseases

As well as viral and fungal diseases, plants are also vulnerable to bacterial infections. Some of the most economically significant of these bacterial plant pathogens are *Pseudomonas syringae*, *Xanthomonas*

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[57] Saunders D G O, Pretorius Z A and Hovmøller M S. 2019 Tackling the re-emergence of wheat stem rust in Western Europe. Commun Biol 2, 51. https://doi.org/10.1038/s42003-019-0294-9

[58] Luo M, Xie L, Chakraborty S *et al*. 2021 *A five-transgene cassette confers broad-spectrum resistance to a fungal rust pathogen in wheat*. Nature biotechnology 39, no. 5:561–566. doi:10.1038/s41587-020-00770-x

[59] Grech-Baran M, Witek K, Poznanski J T, Grupa-Urbanska A, Malinowski T, Lichocka M, Jones J D G and Hennig J. 2022 *The Rysto immune receptor recognises a broadly conserved feature of potyviral coat proteins*. New Phytol 235, no. 3:1179-1195. doi: 10.1111/nph.18183.

[60] Valesquez A C, Mihovilovich E and Bonierbale M. 2007 *Genetic characterization and mapping of major gene resistance to potato leafroll virus in Solanumtuberosum ssp. Andigena*. Theor Appl Genet 114, no. 6: 1051-1058. doi: 10.1007/s00122-006-0498-5.

[61] Salem N M, Jewehan A, Aranda M A and Fox A. 2023 *Tomato brown rugose fruit virus pandemic*. Annu Rev Phytopathol (online). Available at: https://pubmed.ncbi.nlm.nih.gov/37268006/ (accessed 11 July 2023).

[62] Pelletier A and Moffett P. 2022 *N and N'-mediated recognition confers resistance to tomato brown rugose fruit virus*. MicroPubl Biol (online). Available at: https://pubmed.ncbi.nlm.nih.gov/36389119/ (accessed 11 July 2023).

species and *Ralstonia solanacearum*[63]. *R. solanacearum* is estimated to cause US$1 billion in losses each year worldwide in potatoes alone (it can infect over 310 species of plants belonging to 42 plant families).

Immune receptors are often present in some species or plant families but not in others. Plants in the cabbage (Brassicaceae) family have cell-surface immune receptors that recognise a bacterial protein (EF-Tu) found in *Pseudomonas syringae*, *Xanthomonas* species and *R. solanacearum*. *Arabidopsis* (thale cress) carries an immune receptor (EFR) that detects EF-Tu. Transfer of this receptor into tomato confers bacterial wilt resistance[64], and when combined with the Bs2 intracellular immune receptor from pepper that detects a *Xanthomonas* molecule, also confers complete *Xanthomonas* resistance[65]. The EFR immune receptor elevates bacterial resistance in many species[66]. Additional immune receptors that confer *Xanthomonas* and *Ralstonia* resistance can be found in the Australian tobacco *Nicotiana benthamiana*. For example, the *Nicotiana* immune receptor Roq1 detects a protein found in *Pseudomonas*, *Xanthomonas* and *Ralstonia*, and when introduced into tomato using the GM method, Roq1 confers *Ralstonia* resistance[67].

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[63] Mansfield J. Genin S, Magori S, Citovsky V, Sriariyanum M, Ronald P *et al*. 2012. Top 10 plant pathogenic bacteria in molecular plant pathology. Mol. Plant Pathol. 13, 614–629. doi: 10.1111/j.1364-3703.2012.00804.x

[64] Lacombe S, Rougon-Cardoso A, Sherwood E, Peeters N, Dahlbeck D, van Esse H P, Smoker M, Rallapalli G, Thomma B P H J, Staskawicz B, Jones J D G and Zipfel C. 2010 *Interfamily transfer of a plant pattern – recognition receptor confers broad-spectrum bacterial resistance*. Nat. Biotechnol. 28, no. 4: 365-369. doi: 10.1038/nbt.1613.

[65] Kunwar S, Iriarte F, Fan Q, da Silva E E, Ritchie L, Nguyen N S, Freeman J H, Stall R E, Jones J B, Minsavage G V, Colee J, Scott J W, Vallad G E, Zipfel C, Horvath D, Westwood J, Hutton S F and Paret M L. 2018 *Transgenic expression of EFR and Bs2 genes for field management of bacterial wilt and bacterial spot of tomato*. Phytopathology 108, no. 12:1402-1411. doi: 10.1094/PHYTO-12-17-0424-R

[66] Piazza S, Campa M, Popili V, Costa L D, Salvagnin U, Nekrasov V, Zipfel C and Malnoy M. 2021 *The Arabidopsis pattern recongition receptor EFR enhances fire blight resistance in apple*. Hortic Res. 1, no. 8:204. doi: 10.1038/s41438-021-00639-3.

[67] Thomas N C, Hendrich C G, Gill U S, Allen C, Hutton S F and Schultink A. 2020 *The immune receptor Roq1 confers resistance to the bacterial pathogens Xanthomonas, Pseudomonas syringae, and Ralstonia in tomato.* Frontiers in Plant Science 23, no. 11: 463. doi:10.3389/fpls.2020.00463

Resistance to viruses using gene silencing

The examples discussed so far involve the introduction of genes that encode immune receptors that detect pathogen entry and promptly activate the plant's endogenous and effective defence mechanisms. There is another mechanism of disease resistance which involves interfering with the RNA of plant pathogens. This has been successfully used to develop papaya varieties that are resistant to Papaya Ring Spot Virus, a disease that threatened to wipe out commercial papaya production in Hawaii in the 1990s[68]. Over 80% of papaya produced in the US carry this GM trait. The same approach was also used to develop a potato variety that was resistant to potato leaf roll virus, but after initial adoption by potato growers in North America it was withdrawn from the market due to the added complexity of ensuring traceability of GM potatoes in food processing systems[69]. The method was also used in the US to develop squash varieties that are resistant to multiple viruses such as watermelon mosaic virus 2, cucumber mosaic virus and zucchini yellow mosaic virus[70].

These examples demonstrate it is possible to use RNA interference (RNAi) to protect crops against plant viruses. RNAi could also be used to create sugar beet varieties that are resistant to the viruses that cause beet yellows and to protect autumn-sown wheat from barley yellow dwarf virus[71]. It should be emphasized that for many crops such as barley, potato and sugarbeet, the prime rationale for spraying insecticides is to control insects that spread viruses, so virus resistance should significantly reduce the need for insecticide sprays.

Biochemical engineering to elevate disease and pest resistance

A third approach is to identify biochemical pathways in one plant that produce a compound that could provide useful disease control in another plant. For example, wheat is susceptible to the take-all fungus *Geaumannomyces graminis*, whereas oat is not. This resistance has been ascribed to the antifungal molecule avenacin. The entire biosynthetic pathway for making avenacin has now been defined[72] and the 12 genes encoding the enzymes to make avenacin could be transferred to wheat to confer take-all resistance.

Similarly, many plants produce their own compounds that deter herbivorous insects. One such compound is dhurrin which is found

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[68] Ferreira S A, Pitz K Y, Manshardt R, Zee F, Fitch M and Gonsalves D. 2002 *Virus coat protein transgenic papaya provides practical control of papaya ringspot virus in Hawaii*. Plant Dis 86, no. 2:101-105. doi:10.1094/PDIS.2002.86.2.101.

[69] Thornton M. 2004. The Rise and Fall of NewLeaf Potatoes. NABC Rep

[70] National Research Council (US) Committee on Genetically Modified Pest-Protected Plants. 2000 *Genetically Modified Pest-Protected Plants: Science and Regulation*. In Genetically Modified Pest-Protected Plants: Science and Regulation, edited by National Research Council (US), 1-14. Washington, DC: National Academies Press.

[71] Wang M B, Abbott D C and Waterhouse P M. 2000 *A single copy of a virus-derived transgene encoding hairpin RNA gives immunity to barley yellow dwarf virus*. Molecular Plant Pathology 1, no. 6: 347-356. doi: 10.1046/j.1364-3703.2000.00038.x.

[72] Li Y, Leveau A, Zhao Q *et al*. 2021 *Subtelomeric assembly of a multi-gene pathway for antimicrobial defense compounds in cereals*. Nature Communications 12, no. 1:2563. doi: 10.1038/s41467-021-22920-8

in the widely consumed tropical cereal Sorghum. In 2001 scientists in Denmark demonstrated it was possible to transfer the biochemical pathway to produce dhurrin from *Sorghum bicolor* into *Arabidopsis thaliana* and this conferred resistance to flea beetle, a major pest of oilseed rape (OSR) (*Brassica napus*) that is difficult to control without neonicotinoids. *Arabidopsis* is in the brassica family so traits successfully introduced into *Arabidopsis* are likely to be easily transferred to oilseed rape. However, dhurrin accumulation in rapeseed meal might reduce its value for animal feed, so this approach would need to be adopted with care to minimise or mitigate any such consequences.

Another approach is to engineer a plant to express bacterial signalling molecules that disrupt a pathogen's capacity to regulate its virulence[73]; this has proved useful for both *Xanthomonas* and *Xylella* diseases of citrus and would likely be effective against the *Xylella* that is damaging olive orchards in the Mediterranean region[74].

Nematode and insect control using insecticidal proteins or RNAi

Crop plants that incorporate genes from the soil bacterium *Bacillus thuringiensis* (Bt) and produce the Bt protein that deters insect attacks have reduced pesticide use by an estimated 39% in the USA and between 41 – 69% in India[75]. Furthermore, Bt maize reduces damage to cobs through which mycotoxin-producing fungi enter, thus reducing mycotoxins in the human diet[76].

Farmers were able to choose to apply fewer pesticides because Bt crops enabled them to do so. However, when access to chemical control measures is restricted, such as the bans on neonicotinoids in the UK and EU[77], without access to genetic solutions, farmers can give up growing certain crops. This is exemplified by oilseed rape whose area of production in the UK has declined by 59%[78] between 2012 (the year before the first EU-wide restrictions on use of three neonicotinoids in crops including oilseed rape that are attractive to bees[79]) and 2021[80].

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[73] Caserta R, Souza-Neto R R, Takita M A, Lindow S E and De Souza A A. 2017 *Ectopic Expression of Xylella fastidiosa rpfF Conferring Production of Diffusible Signal Factor in Transgenic Tobacco and Citrus Alters Pathogen Behavior and Reduces Disease Severity*. Molecular plant-microbe interactions : MPMI, 30(11), 866–875. https://doi.org/10.1094/MPMI-07-17-0167-R

[74] Schneider K, van der Werf W, Cendoya M, Mourits M, Navas-Cortés J A, Vicent A and Oude Lansink A. 2020 *Impact of Xylella fastidiosa subspecies pauca in European olives*. Proceedings of the National Academy of Sciences of the United States of America, 117(17), 9250–9259. https://doi.org/10.1073/pnas.1912206117

[75] National Academies of Sciences, Engineering, and Medicine. 2016 *Genetically Engineered Crops: Experiences and Prospects*. Washington, DC: The National Academies Press.

[76] Wu F. 2006 *Mycotoxin Reduction in Bt Corn: Potential Economic, Health, and Regulatory Impacts.* Transgenic Research 15, no. 3: 277-289. doi: 10.1007/s11248-005-5237-1.

[77] UK Parliament. 2023 *Chemical Regulation after Brexit: REACH*. House of Commons Library Research Briefing CDP-2023-0025 (online). Available at: https://commonslibrary.parliament.uk/research-briefings/cdp-2023-0025/#:~:text=January%202023%20updates%3A&text=See%3A%20Chemical%20and%20Engineering%20News,industry%20strongly%20criticised%20the%20ruling (accessed 15 June 2023).

[78] Calculation based on data from the National Statistics on Cereal and oilseed rape production available from: https://www.gov.uk/government/statistics/cereal-and-oilseed-rape-production

[79] European Commission. 2023 *Neonicotinoids*. Food, Farming, Fisheries (online). Available at: https://food.ec.europa.eu/plants/pesticides/approval-active-substances/renewal-approval/neonicotinoids_en (accessed 15 June 2023).

[80] 2021 is the last year with complete data available when accessed on 15 June 2023.

This decline means the UK is now a net importer of rapeseed oil (the most widely used vegetable oil) having previously been a net exporter[81]. Where oilseed rape is still grown in the UK, farmers have increased their use of pyrethroid insecticides which are both more toxic to non-target insects and less effective at killing target insects[82]. Using the GM method to introduce Bt proteins to oil seed rape could provide a less environmentally harmful means of pest control. Although more frequently used against *Lepidoptera* pests (moths), some Bt proteins are effective against larvae of *Coleoptera*[83] (beetles) such as the flea beetle. The current regulatory burden, and the negative perception surrounding use of the GM method, might partially explain why this simple approach is not being investigated. Bt protein expression should also protect Brassica crops from caterpillars of the cabbage white butterfly, benefitting both horticultural producers and home gardeners.

Whiteflies are major virus vectors, and whitefly resistance in cotton was achieved when an insecticidal protein from an edible fern was expressed[84]. *Tectaria macrodonta* (*syn. T. coadunata*) is widely consumed in Nepal and has been assessed for its nutritional qualities in the human diet[85, 86]. Ferns are very resistant to whitefly. A "Tma12" protein was identified in *T. macrodonta* that when expressed in cotton, confers strong resistance to whitefly. As whitefly is a vector for viral diseases of food crops, the efficacy of the Tma12 protein in deterring whitefly in cotton and the fact that the source of this protein has a history of safe consumption suggests that the trait could be used effectively to provide whitefly resistance in a range of food crops.

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[81] United States Department of Agriculture (USDA). 2022 *Oilseeds and Products Annual: London, United Kingdom*. UK2022-0019 (online). Available at: https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=Oilseeds%20and%20Products%20Annual_London_United%20Kingdom_UK2022-0019.pdf (accessed 15 June 2023).

[82] Kathage J, Castañera P, Alonso-Prados J L, Gómez-Barbero M and Rodríguez-Cerezo E. 2018 *The impact of restrictions on neonicotinoid and fipronil insecticides on pest management in maize, oilseed rape and sunflower in eight European Union regions*. Pest Manag Sci 74, no. 1: 88-99. doi: 10.1002/ps.4715.

[83] Domínguez-Arrizabalaga M, Villanueva M, Escriche B, Ancín-Azpilicueta C, Caballero P. 2020 *Insecticidal activity of Bacillus thuringiensis proteins against coleopteran pests*. Toxins (Basel) 29, no. 7: 430. doi: 10.3390/toxins12070430.

[84] Shukla A, Upadhyay S, Mishra M *et al*. 2016 *Expression of an insecticidal fern protein in cotton protects against whitefly*. Nature biotechnology, 34(10), 1046–1051. https://doi.org/10.1038/nbt.3665

[85] Smriti Chettri. 2018 *Nutrient and Elemental Composition of Wild Edible Ferns of the Himalaya.* American Fern Journal, 108(3), 95-106, https://doi.org/10.1640/0002-8444-108.3.95

[86] Bajracharya G B and Bajracharya B. 2022 *A comprehensive review on Nepalese wild vegetable food ferns*. Heliyon, 8(11), e11687. https://doi.org/10.1016/j.heliyon.2022.e11687

Researchers are also exploring the potential of the RNAi approach to protect against parasitic nematodes[87], a major class of crop pests that are estimated to cause \$80 – \$118 billion US dollars per year in damage[88].

GM methods to facilitate weed control

Competition from weeds results in an estimated 30 – 34% of total yield losses[89]. Ploughing to prevent weed competition is estimated to increase greenhouse gas emissions by 30% compared with no-till systems in the UK[90] and also causes soil compaction and tractor CO_2 emissions. One of the most common current uses of the GM method is to help farmers control weeds. A challenge for weed control is how to reduce growth of the weeds without impacting growth of the crop. Some selective herbicides act more strongly against broad-leaf plants than grasses, enabling their deployment in cereal crops. However, non-selective herbicides act equally against weed and crop by inhibiting plant amino acid biosynthesis. One such herbicide is glyphosate, which inhibits an enzyme required for producing aromatic amino acids (tryptophan, phenylalanine and tyrosine). This enzyme is absent in mammals, significantly reducing potential risk to humans from glyphosate. Sulfonylurea-based herbicides also inhibit an enzyme (specifically acetolactate synthase required for branched chain amino acid biosynthesis) that is not found in humans and animals.

To enable the application of these herbicides without damaging the crops, it is possible to add herbicide resistance genes to crops. These genes either encode an enzyme that is not inhibited by the herbicide, or that detoxifies the herbicide. Herbicide tolerance traits have enabled the substitution of more persistent herbicides with glyphosate[91]. This has reduced dependence on ploughing for weed control ('no-till agriculture') and so provided considerable benefits in soil carbon sequestration. Although there is a widespread perception that glyphosate carries human health risks, the European Food Safety Authority's review of the impact of glyphosate on the health of humans, animals and the environment did not "identify any critical areas of concern in its peer review of the risk assessment of the active substance glyphosate in relation to the risk it poses to humans and animals or the environment"[92].

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[87] Banerjee S, Banerjee A, Gill SS, Gupta OP, Dahuja A, Jain PK and Sirohi A. 2017 *RNA Interference: A Novel Source of Resistance to Combat Plant Parasitic Nematodes*. Front Plant Sci. 19, no. 8: 834. doi: 10.3389/fpls.2017.00834.

[88] Bernard G C, Egnin M and Bonsi C. 2017 *The impact of plant-parasitic nematodes on agriculture and methods of control. Nematology-concepts, diagnosis and control, 10*, pp.121 – 151. Intechopen: Nigeria.

[89] Zimdahl R L. 2018 *Fundamentals of weed science*. Academic press.

[90] Cooper H V, Sjogersten S, Lark R M and Mooney S J. 2021 *To till or not to till in a temperate ecosystem? Implications for climate change mitigation*. Environmental Research Letters, 16, 054022, https://doi.org/10.1088/1748-9326/abe74e.

[91] Brookes G and Barfoot P. 2020 *Environmental impacts of genetically modified (GM) crop use 1996 – 2018: impacts on pesticide use and carbon emissions*. GM crops & food, 11(4), 215 – 241. https://doi.org/10.1080/21645698.2020.1773198

[92] European Food Safety Authority. 2023 *Glyphosate: no critical areas of concern; data gaps identified* (online). Available at: https://www.efsa.europa.eu/en/news/glyphosate-no-critical-areas-concern-data-gaps-identified#:~:text=EFSA%20did%20not%20identify%20any,and%20animals%20or%20the%20environment (accessed 8 August 2023).

However there is evidence that extensive deployment of this weed control method has selected for herbicide tolerance in weeds. This has been exacerbated by lack of rotation of deployment of the trait. In the predominant maize/soybean rotational scheme in the US, if both crops are glyphosate resistant, selection for herbicide resistant weeds is relentless, accelerating the evolution of resistant weeds.

As well as weed control, herbicide resistance has also been used to facilitate hybrid seed production in crops such as oilseed rape. This approach was recently approved in India for hybrid seed production in oilseed mustard (*Brassica juncea*). Hybrid seed production is important for increasing yields, which can be as much as 20% higher than the parent lines from which hybrids are produced. Producing fertile hybrid seed is difficult but can be facilitated by identifying plants with the specific genes necessary for effective hybridisation. By linking these genes to herbicide resistant genes and then spraying the crop with herbicide it is possible to identify plants that have the specific combination of genes required[93]. This method is widely adopted for hybrid seed of oilseed rape (also known as canola) in the US, Canada and Australia.

Phosphite utilisation
An alternative to using herbicides for weed control is to give the crops a comparative growth advantage against weeds. Phosphorus is an important element for plant growth and is typically supplied in the form of phosphate fertilisers to increase yields. However, these fertilisers also encourage the growth of weeds in fields and phosphate run-off can lead to algal growth in watercourses, resulting in a die-off of other aquatic life due to a lack of oxygen.

Some soil bacteria have evolved to be able to use an alternative form of phosphorus, phosphite instead of phosphate. Plants cannot typically absorb this form of phosphorus but scientists in Mexico showed that introducing the *PtxD* gene from the soil bacterium *Pseudomonas stutzeri* into rice and cotton enables the crop plant to use phosphite[94]. When genetically modified rice was grown fertilised by phosphite it produced the same yield as unmodified rice fertilised with phosphate. Since the weeds cannot use phosphite, if phosphite is the sole phosphorus source, this provides an advantage for the crop and helps control weeds without needing herbicides. This could reduce the need for the herbicide tolerant traits described in the previous section.

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[93] Shukla P, Singh N K, Gautam R, Ahmed I, Yadav D, Sharma A and Kirti P B. 2017 *Molecular Approaches for Manipulating Male Sterility and Strategies for Fertility Restoration in Plants*. Molecular biotechnology, 59(9-10), 445 – 457. https://doi.org/10.1007/s12033-017-0027-6

[94] Pandeya D, López-Arredondo D L, Janga M R, Campbell L M, Estrella-Hernández P, Bagavathiannan M V, Herrera-Estrella L and Rathore K S. 2018 *Selective fertilization with phosphite allows unhindered growth of cotton plants expressing the ptxD gene while suppressing weeds*. Proceedings of the National Academy of Sciences of the United States of America, 115(29), E6946 – E6955. https://doi.org/10.1073/pnas.1804862115

Improved mineral nutrition and photosynthesis

Improved mineral uptake and nitrogen fixation in cereal crops

Dwarf crop varieties developed during the ‘Green Revolution’ that began in the 1960s showed increased yields in part because they could tolerate higher applications of synthetic fertilisers without falling over (‘lodging’). These fertilisers contribute to climate change through greenhouse gas emissions associated with both their production and the generation of nitrous oxide from reactions with soil microorganisms. Agricultural uses of nitrogen fertilisers, both synthetic and organic, contribute to harmful air pollution in the form of ammonia and ammonium-containing fine particulate matter[95], and the application of synthetic fertilisers is associated with both reduced soil biodiversity[96] and aquatic biodiversity where fertiliser runs off into local water courses[97].

When nutrient availability is low, many plants form symbiotic relationships with soil fungi to increase their access to nutrients. These fungal networks act like an extension of the plant’s roots, providing nutrients like nitrogen, phosphorous and water in return for sugars made by the plant through photosynthesis. If plants can meet their nutritional needs without the help of fungi, they suppress this relationship, but this reduces the efficiency of their nutrient uptake. This reduced efficiency means that farmers have to provide more nutrients than the plants can use, which increases the environmental impact associated with this input usage.

To address this, researchers at the Crop Science Centre (CSC) in Cambridge are testing GM barley lines modified with a gene from a leguminous plant (*Medicago truncatula*) that maintains a symbiotic relationship with soil fungi even when they have access to high levels of phosphorus[98]. If these field trials prove successful, this raises the prospect of cereals that can use inputs more efficiently and so require less to be applied. Because of the regulatory hurdles faced by GM crops, these researchers are also testing whether they can achieve the same outcome without moving genes between species.

Although increased nitrogen use efficiency would be helpful, removing the need to apply it at all would be even better. Leguminous crops (peas, broad beans, lentils etc) do not depend on fertiliser application as they can ‘fix’ nitrogen directly from the atmosphere via a symbiotic relationship with soil bacteria that form nodules in the roots of these plants and convert gaseous nitrogen (N_2) into ammonia (NH_3). Researchers at the CSC have helped define the genes in legumes that enable this interaction with nitrogen-fixing

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[95] Guthrie S, Giles S, Dunkerley F, Tabaqchali H, Harshfield A, Ioppolo B and Manville C. 2018 *The Impact of Ammonia Emissions from Agriculture on Biodiversity*. Cambridge, UK: RAND Corporation and The Royal Society.

[96] Tripathi S, Sriavastava P, Devi R S and Bhadouria R. 2020 *Influence of Synthetic Fertilisers and Pesticides on Soil Health and Soil Microbiology*. In Prasad, M.N.V. (Ed.), Agrochemicals Detection, Treatment and Remediation: Pesticides and Chemical Fertilisers, 25-54. Hyderabad: Elsevier Ltd.

[97] Jwaideh M A A, Sutanudjaja E and Dalin C. 2022 *Global impacts of nitrogen and phosphorous fertiliser use for major crops on aquatic biodiversity*. The International Journal of Lifecyle Assessment 27, no. 2: 1048-1080. doi: 10.1007/s11367-022-02078-1.

[98] Li XR, Sun J, Albinsky D *et al*. 2022 *Nutrient regulation of lipochitooligosaccharide recognition in plants via NSP1 and NSP2*. Nat Commun 13:6421. https://doi.org/10.1038/s41467-022-33908-3

bacteria and are engineering this capability into cereal crops such as wheat and barley by transferring genes from legumes.

This is a complicated challenge and the researchers estimate that it will take at least 10 years. If it were achieved, it will be of particular benefit to farmers in low-income countries who cannot afford fertilisers.

Increasing Photosynthetic Efficiency

Another determinant of yield is the efficiency with which plants convert solar energy into sugars through photosynthesis. Photosynthesis is a complex process involving at least 170 steps. An international team of researchers is working to understand the genetic basis of these steps to inform strategies that can increase the proportion of solar energy that is converted into plant growth.

One such strategy is to accelerate the speed with which photosynthesis readjusts from photoprotection as leaves in dense crop canopies transition from full sunlight to shade. Models of crop canopy photosynthesis predict that this slow adjustment costs 20 – 40% of potential productivity. Researchers at the Universities of Illinois and California Berkeley have developed a variety of soya bean that has been genetically modified so that the photoprotection mechanism that inhibits photosynthesis readjusts more rapidly on transition to shade. In field trials these GM beans yielded over 20% more than conventional varieties with no impact on protein content[99]. This follows earlier work that demonstrated a 20% increase in productivity with the same GM improvement in tobacco in field trials[100].

Another strategy that has demonstrated significant enhancement in photosynthetic efficiency involves reducing losses that result from photorespiration[101]. A third research program at the University of Essex achieved elevated photosynthetic efficiency by overexpressing the photosynthetic enzyme sedoheptulose bisphosphatase[102]. These and other approaches were assessed recently in an authoritative review[103]. A valuable recent commentary emphasised the necessity for professionally conducted large scale field trials before claims of large yield increases can be considered as fully justified[104].

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[99] De Souza A P, Burgess S J, Doran L, Hansen J, Manukyan L, Maryn N, Gotarkar D, Leonelli L, Niyogi K K and Long S P. 2022 *Soybean photosynthesis and crop yield are improved by accelerating recovery from photoprotection*. Science 377:851-854. doi: 10.1126/science.adc9831.

[100] Kromdijk J, Głowacka K, Leonelli L, Gabilly S T, Iwai M, Niyogi K K and Long S P 2016 *Improving photosynthesis and crop productivity by accelerating recovery from photoprotection*. Science 354: 857–861. doi: 10.1126/science.aai8878.

[101] South P F, Cavanagh A P, Liu H W and Ort D R. Synthetic glycolate metabolism pathways stimulate crop growth and productivity in the field. Science (New York, N.Y.), 363(6422), eaat9077. https://doi.org/10.1126/science.aat9077

[102] López-Calcagno P E, Brown K L, Simkin A J, Fisk S J, Vialet-Chabrand S, Lawson T and Raines C A. 2020 *Stimulating photosynthetic processes increases productivity and water-use efficiency in the field*. Nature plants, 6(8), 1054–1063. https://doi.org/10.1038/s41477-020-0740-1

[103] Smith E N, van Aalst M, Tosens T, Niinemets Ü, Stich B, Morosinotto T, Alboresi A, Erb T, Gómez-Coronado P A, Tolleter D, Finazzi G, Curien G, Heinemann M, Ebenhöh O, Hibberd J M, Schlüter U, Sun T and Weber A P M. 2023 *Improving photosynthetic efficiency toward food security: Strategies, advances, and perspectives*. Mol. Plant. doi: https://doi.org/10.1016/ j.molp.2023.08.017.

[104] Khaipho-Burch M, Cooper M, Crossa J, de Leon N, Holland J, Lewis R, McCouch S, Murray S C, Rabbi I, Ronald P, Ross-Ibarra J, Weigel D and Buckler, E S 2023 *Genetic modification can improve crop yields – but stop overselling it*. Nature, 621(7979), 470–473. https://doi.org/10.1038/d41586-023-02895-w

The UK spin-out company Wild Bioscience[105] has also engineered plants with elevated photosynthetic efficiency by altering the expression of a regulator of the photosynthetic machinery in the leaf. This results in a significant increase in yield in *Arabidopsis*, and field trials to test this technology in wheat are currently ongoing[106].

Replacing ferredoxin with flavodoxin to enhance tolerance to stress and iron deprivation

A stress-sensitive iron-sulphur protein called ferredoxin is an important component of the photosynthetic machinery of plant chloroplasts that powers carbon assimilation in leaves. However, stress or iron depletion lowers levels of ferredoxin, inhibiting photosynthesis and promoting photo-oxidative stress. When ferredoxin was supplemented in tobacco by using the GM method to engineer accumulation in chloroplasts of a protein with the same function – a flavodoxin that does not contain iron from blue-green algae – the resulting transgenic lines show broad enhancement in tolerance to drought, chilling, oxidants, heat and iron starvation[107].

Adaptation to environmental change

The interlinked crises of climate change and biodiversity loss are imposing additional challenges for crop production. Responding to this disruption requires crops that can cope with increasingly extreme weather events, particularly drought.

Enhanced drought-tolerance

With many parts of the world facing increased water stress as a result of population growth and climate change, increasing the productivity of crops in periods of low water availability is a major plant-breeding objective. In the 1990s, publicly-funded researchers in Argentina were analysing the genes in sunflowers that enabled them to tolerate variations in their growing conditions better than other plants. They identified the *HB4* gene as playing a crucial role in sunflowers' ability to keep growing during periods of low water availability. In 2004 they entered into a partnership with an Argentinian biotechnology company (Bioceres Crop Solutions) to work on introducing this drought-tolerance trait to major crop species such as wheat and soya beans.

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[105] Wild Bioscience (online) Available at: https://www.wildbioscience.com/ (accessed 11 July 2023).

[106] WIPO. 2021 *WO2021234370 – Enhancement of productivity in C3 Plants* (online). Available at: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021234370 (accessed 11 July 2023).

[107] Zurbriggen M D, Tognetti V B, Fillat M F, Hajirezaei M R, Valle E M and Carrillo N. 2008 *Combating stress with flavodoxin: a promising route for crop improvement*. Trends in biotechnology, 26(10), 531 – 537. https://doi.org/10.1016/j.tibtech.2008.07.001

In 2020 Bioceres received approval in Argentina for cultivation of wheat to which the sunflower *HB4* gene had been added using the GM method. This wheat yields 20% more than unmodified varieties during growing seasons affected by drought[108]. This wheat has been approved for human consumption in Australia, Brazil, Colombia, New Zealand, Nigeria and the USA, and was approved for cultivation in Brazil in 2023. Several countries have also approved soya beans modified with the same *HB4* gene to be drought resistant and Bioceres is looking to licence the technology to other plant breeders to increase the range of drought tolerant crops.

Improved nutritional content

The GM trait examples discussed above help address challenges faced by food producers and reduce environmental impacts. The GM method is also increasingly being used for traits that are of direct benefit to consumers. Most of those relate to nutrition but there are also examples relevant to cleaning up the toxic legacies of heavy industry or war.

Whilst there is widespread agreement that the best way to meet our nutritional needs is to eat a wide variety of foods, mostly fruit and vegetables[109], many people's diets, especially in low-income countries, are dependent on carbohydrate-rich foods to get the calories they need at a price they can afford. Unfortunately, people that depend on such diets often suffer poor health caused by nutrient deficiencies. Zinc deficiency alone is thought to cause over 400,000 deaths worldwide per year[110]. Increasing the nutritional content of dietary staples such as rice and wheat is one way to ensure that people in all countries who cannot afford to eat a balanced diet get more of the nutrients they need.

Vitamin A enriched rice

Perhaps the best known example of using the GM method to increase the nutritional content of food is vitamin A enriched rice. Vitamin A deficiency is the leading cause of preventable blindness in children and also compromises immune system function, increasing the risk of disease and death from severe infections. In some countries, rice can make up the majority of food that children eat. In the 1990s scientists in Switzerland and Germany first showed that rice can be genetically modified to accumulate high levels of beta-carotene in the endosperm (the part of the rice grain that people eat). Beta carotene is metabolised by humans into vitamin A and confers on the modified rice an orangey-yellow colour which led it to be called Golden Rice. Subsequent research has increased levels of beta-carotene in the grain and introduced this trait into rice varieties that are widely grown in parts of the world with a high incidence of vitamin A deficiency.

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[108] Nature Biotechnology. 2021 *Argentina first to market with drought-resistant GM wheat*. Nature Biotechnology: News in Brief 39:652. doi: https://doi.org/10.1038/s41587-021-00963-y.

[109] Gonzalez Fischer C and Garnett T. 2016 *Plates, pyramids, planet. Developments in national healthy and sustainable dietary guidelines: a state of play assessment*. Food and Agriculture Organisation of the United Nations, The Food Climate Research Network at The University of Oxford. (online). Available at: https://www.fao.org/sustainable-food-value-chains/library/details/en/c/415611/ (accessed 12 July 2023).

[110] Fischer Walker C, Ezzati M and Black R. 2009 *Global and regional child mortality and burden of disease attributable to zinc deficiency*. Eur J Clin Nutr 63, 591–597. https://doi.org/10.1038/ejcn.2008.9

The Philippines was the first country to approve a golden rice variety for commercial cultivation and in 2022, farmers there harvested almost 70 tonnes which was distributed to households with pregnant women, breastfeeding mothers or preschool children who are at risk of diseases caused by vitamin A deficiency[111]. However, at the time of writing, distribution of these improved varieties has been put on hold due to legal challenges[112].

Iron and zinc fortified wheat

Another staple that is being targeted for improvement is wheat. Researchers at the John Innes Centre have been working on increasing the iron and zinc content of wheat in a way that raises the concentration of these nutrients in white flour made with those genetically modified grains more than twofold[113]. This avoids the need to fortify white flour with iron. First efforts to achieve this outcome did not depend on genes from another species but did depend on combining genetic sequences from within the wheat genome in a way that cannot be achieved with traditional breeding or gene editing. Further improvements were achieved by adding a gene from rice[114]. The team will conclude their field trials in 2024 and if successful, their material could be made immediately available to plant breeders developing wheats for parts of the world with a high burden of disease from iron and zinc deficiencies.

Production of omega 3 long-chain polyunsaturated fatty acids in *Camelina sativa*

Long chain omega-3 fatty acids are important for human health and have to be sourced from the food we eat as humans cannot make them. Two of the three main omega-3s (Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) are made by marine algae and are sourced primarily from oily fish. These sources are under pressure as many wild fisheries are 'over exploited'[115], and levels of these fatty acids in farmed fish are declining as fish farmers seek to reduce their dependence on wild fish by using alternative feeds derived from plants or insects.

To provide an alternative source of these essential fatty acids, scientists at Rothamsted Research in Hertfordshire have introduced genes from marine algae that encode enzymes that make these fatty acids into *Camelina sativa*, a plant grown as a source of vegetable oil. The research team has demonstrated that the novel oil is safe for direct human

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[111] Ruegg P. 2022 *For the first time, farmers in the Philippines cultivated Golden Rice on a larger scale and harvested almost 70 tons*. Phys.org (online). Available at: https://phys.org/news/2022-11-farmers-philippines-cultivated-golden-rice.html (accessed 19 April 2023).

[112] CNN Philippines. 2023 *SC orders stop to commercial release of genetically modified rice, eggplant products* (online). Available at: https://www.cnnphilippines.com/news/2023/4/19/stop-commercial-release-rice-eggplant.html (accessed 9 May 2023).

[113] Harrington S A, Connorton J M, Nyangoma N I M *et al*. 2023 *A two-gene strategy increases iron and zinc concentrations in wheat flour, improving mineral bioaccessibility*. Plant physiology, 191(1), 528–541. https://doi.org/10.1093/plphys/kiac499

[114] John Innes Centre, FAQs: Planned field trial of high-iron wheat (online). Available at: https://www.jic.ac.uk/research-impact/planned-field-trial-of-high-iron-wheat/ (accessed 6 September 2023).

[115] Ritchie H and Roser M. 2021 *Fish and overfishing* Our world in data (online). Available: https://ourworldindata.org/fish-and-overfishing#how-is-overfishing-changing-over-time (accessed 2 May 2023).

consumption and taken up by cells in the same way as equivalent fatty acids from fish oils[116].

As farmed fish are expected to provide an important source of protein, the researchers have also been working with the Institute of Aquaculture at the University of Stirling to develop feeds from these genetically modified vegetable oils and demonstrated they are a safe and effective substitute for oceanic-derived fish oils[117].

Increased anthocyanins in tomatoes
Polyphenols in our diets promote health. Anthocyanins – the compounds responsible for the red, purple and blue colours in fruits such as blackcurrants and vegetables such as red cabbage and aubergine – are sources of these compounds. Dietary anthocyanins and other polyphenols have been reported to reduce the risk of certain cancers and cardiovascular disease[118].

Scientists at the John Innes Centre have developed a purple tomato which has high levels of anthocyanin in the flesh as well as the skin. This was achieved by introducing two regulatory genes from the common ornamental flowering plant snapdragon. In a feeding trial using mice that had been bred to have an increased risk of cancer, mice fed with the purple tomato lived 30% longer than mice fed with conventional tomatoes[119]. Anthocyanins also play a role in how long fruit and vegetables last once they have been harvested and tomatoes that have elevated levels of anthocyanins have twice the shelf life of their conventional counterparts[120]. Increased shelf-life is important for reducing food waste. The GM tomato developed by UK scientists was approved for commercial cultivation in the USA in 2022 under the US Department of Agriculture's new *Regulatory Status Review* framework as discussed in Chapter 3. The Purple Tomato also received approval from the US Food and Drug Administration in July 2023.

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[116] West A L, Miles E A, Lillycrop K A, Napier J A, Calder P C and Burdge G C. 2021 *Genetically modified plants are an alternative to oily fish for providing n-3 polyunsaturated fatty acids in the human diet: A summary of the findings of a Biotechnology and Biological Sciences Research Council funded project*. Nutr Bull 46:60-68. https://doi.org/10.1111/nbu.12478.

[117] Napier J A and Betancor M B. 2023 *Engineering plant-based feedstocks for sustainable aquaculture*. Current Opinion in Plant Biology 71:102323. doi: 10.1016/j.pbi.2022.102323.

[118] Vasantha Rupasinghe H P and Arumuggam N. 2019 *Health benefits of anthocyanins*, in M. Su-Ling Brooks & G.B. Celli (Eds.) Anthocyanins from Natural Sources: Exploiting Targeted Delivery for Improved Health. London: Royal Society of Chemistry :121 – 158.

[119] Butelli E, Titta L, Giorgio M *et al*. 2008 *Enrichment of tomato fruit with health-promoting anthocyanins by expression of select transcription factors*, Nature Biotechnology 26 ,1301–1308. (doi:10.1038/nbt.1506)

[120] Zhang Y, Butelli E, De Stefano R, Schoonbeek HJ, Magusin A, Pagliarani C, Wellner N, Hill L, Orzaez D, Granell A and Jones J D. 2013 *Anthocyanins double the shelf life of tomatoes by delaying overripening and reducing susceptibility to gray mold*, Current Biology. 23,1094-1100. (doi:10.1016/j.cub.2013.04.072)

Reduced acrylamide accumulation in starch-based foods cooked at high temperature

During high temperature (>120°C) cooking (roasting or frying in oil, rather than boiling), if the reducing sugars glucose or fructose and the amino acid asparagine are present in a starchy food, the toxic and probably carcinogenic compound acrylamide is formed via the Maillard reaction[121]. Potatoes and wheat are starchy foods that are processed into products such as French fries (chips) and crisps or bread. Levels of acrylamide in these products can be reduced if levels of asparagine or reducing sugars are reduced in the source tubers or grains either by the GM method or using gene editing.

The Simplot company in the US has lowered levels of reducing sugars in potato by tuber-specific silencing (using RNAi) of a gene encoding the invertase enzyme that converts sucrose to glucose and fructose, especially in potatoes that are stored in the cold. They also silenced specifically in the tuber a polyphenol oxidase enzyme that is associated with bruise damage to tubers that result in food waste. These traits are approved in the US and are incorporated into some of the potato late blight resistant lines developed at TSL, and also combined with late blight resistance in approved products in the US[122].

There would be considerable potential benefits to human health from reducing acrylamide accumulation in processed products if these traits were approved in potato and wheat.

Remediation of contaminated land

The GM method has also been used to develop plants that are able to clean up polluted environments[123]. Contaminants that plants can metabolise or remove from soils and lock away in their tissues include heavy metals like cadmium, metalloids like arsenic, and persistent organic pollutants[124]. One category of these persistent pollutants is residues from explosives. These are concentrated in warzones and military firing ranges from where they can leach out into local watercourses and groundwater, presenting a risk to humans, animals and soil microbiota.

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[121] NIH National Cancer Institute, Acrylamide and Cancer Risk (online) Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/acrylamide-fact-sheet (accessed 19 October 2023).

[122] Simplot. 2021 *Request for a Regulatory Status Review for BG25 Potato* (online). Available at: https://www.aphis.usda.gov/brs/pdf/rsr/21-270-01rsr-review-submission.pdf (accessed 19 October 2023).

[123] Fasani E, Manara A, Martini F, Furini A and DalCorso G. 2018 *The potential of genetic engineering of plants for the remediation of soils contaminated with heavy metals*. Plant, cell & environment, 41(5), 1201–1232. https://doi.org/10.1111/pce.12963

[124] Rylott E L and Bruce N C. 2022 *Plants to mine metals and remediate land*. Science 377:1380-1381. doI:10.1126/science.abn6337

To address this, researchers at the University of York's Centre for Novel Agricultural Products have demonstrated the ability to develop plants that can metabolise explosive residues using genes from soil bacteria. Working with the US Department of Defence they have conducted 3-year field trials on a US military site which demonstrated that a genetically modified native grass species *(Panicum virgatum*) can effectively remediate soils contaminated with explosive residues[125]. While the researchers acknowledge that using this approach to clean up the much more widespread pollution in warzones will be more complicated than defined training ranges, they are working on approaches that would be suitable for this.

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[125] Cary T J, Rylott E L, Zhang L, Routsong R M, Palazzo A J, Strand S E and Bruce N C, 2021 *Field trial demonstrating phytoremediation of the military explosive RDX by XplA/XplB-expressing switchgrass*. Nat Biotechnol 39:1216–1219 doi: https://doi.org/10.1038/s41587-021-00909-4

ANNEX B

Guidance on the USDA *Regulatory Status Review* process

This annex provides guidance to developers of genetically modified plants from the United States Department of Agriculture Animal and Plant Health Inspection Service on the *Regulatory Status Review* process for assessing the plausibility of a GMO presenting a plant pest risk

Under this framework plant breeders provide the regulator with information about the plant they have modified, the trait they have introduced, and the mechanism of action. The regulator then uses the information provided by the breeder, publicly available information, and its knowledge and experience with the plant, trait, and mechanism of action to conduct an initial review. This assessment is done relative to a 'comparator plant', which is likely to be the breeding line in which a genetic change was made to create the genetically modified organism or, for nutritional traits, to a range of values in current commercially available varieties.

The review considers the biology of the comparator plant (and its sexually compatible relatives, if applicable), the trait and mechanism of action, and the effect of the trait and mechanism of action on:

- the distribution, density, or development of the plant and its sexually compatible relatives;
- the production, creation, or enhancement of a plant pest or a reservoir for a plant pest;
- harm to non-target organisms beneficial to agriculture; and
- the weedy impacts of the plant and its sexually compatible relatives.

To support this analysis, the regulator relies on two internal reference documents, a Plant Reference Document (PRD), and a Mechanism of Action Description. The PRD documents the following information:

- The taxonomy and sexually compatible relatives of a plant.
- Its agroecology including domestication history and use, where it is cultivated in the US.
- The agronomic practices used in cultivation of the plant.
- The occurrence pattern of the plant, with and without intentional human assistance.
  - A model of the climatic suitability for the plant (ie, where general climatic conditions (ie, the average climatic conditions over time) could enable the plant to complete a normal life cycle).
- A synthesis section that concludes which biological properties could change the occurrence of the plant if they were altered by genetic modification.
- The following impacts of the plant:
  - Impacts on non-target organisms beneficial to agriculture.
  - Impacts mediated by plant pests and pathogens.
  - Impacts on agricultural productivity or quality.
  - Impacts on agriculturally important natural resources including plant communities and hydrology.

Mechanism of Action Descriptions (MOADs) summarise key information about the mechanism of action, including the biochemical action of the introduced or modified genetic material and its metabolic, physiological and/or developmental functions, as well as the intended and any previously observed or plausible changes that could occur as a result of introducing or modifying the genetic material. The MOAD identifies whether there is a linkage between the Mechanism of Action and any of the biological properties discussed in the PRD or adverse consequence associated with plant pest risk, whether there are potential changes in occurrence of the modified plant relative to the comparator, and whether any identified potential occurrence change or linkage to an adverse consequence justifies a plausible pathway to increased plant pest risk.

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Jonathan Jones FRS has a commercial interest in Mendel Biotechnology, Norfolk Plant Science, and GenXtraits.

Jonny Hazell has no relevant commercial interests.

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