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Review

Insights on cisgenic plants with durable disease resistance under the European Green Deal

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Significant shares of harvests are lost to pests and diseases, therefore, minimizing these losses could solve part of the supply constraints to feed the world. Cisgenesis is defined as the insertion of genetic material into a recipient organism from a donor that is sexually compatible. Here, we review (i) conventional plant breeding, (ii) cisgenesis, (iii) current pesticide-based disease management, (iv) potential economic implications of cultivating cisgenic crops with durable disease resistances, and (v) potential environmental implications of cultivating such crops; focusing mostly on potatoes, but also apples, with resistances to *Phytophthora infestans* and *Venturia inaequalis,* respectively. Adopting cisgenic varieties could provide benefits to farmers and to the environment through lower pesticide use, thus contributing to the European Green Deal target.

Food systems in a changing (regulatory) landscape

The increasing demand and a changing climate challenge our **food systems** (see Glossary) globally [1–4]. In the last decade, the population growth rate significantly outpaced yield improvements in grains across the world [5]. At the same time, societal concerns on the environmental burden associated with agricultural production and input use rightfully question current farming practices [6,7]. Preventing losses in harvests to pests has great potential, as significant amounts of global harvests are lost to pests and diseases [8,9].

While farmers apply a multitude of agronomic strategies to minimize pest and disease impacts, a key tool remains the use of **pesticides** [10,11]. Farmers apply millions of tonnes of pesticides on fields across the world each year [11] (see Table S1 in the supplemental information online). The consequences for the environment and human health from misuse of these chemicals are of societal concern [12,13]. Pesticide residues are found in soils, surface water, groundwater, non-target plants, food and feed, animals, and humans [10,11,14]. While pesticide-related contamination of food beyond the maximum residue limit are generally rare in Europe [15], a reduction in pesticide use may nevertheless contribute to human health through a lower exposure, in particular of agricultural workers and citizens living in proximity to agricultural fields [16].

To address societal concerns, under the European Green Deal, the Farm to Fork (F2F) strategy and the Biodiversity Strategies set the ambitious objective of reducing the use and risk of chemical pesticides, as well as the use of more hazardous pesticides, by 50% by 2030[i]. Without adapting food production systems, halving pesticide use and risk may result in sizable reductions in yields, which could affect European consumers as well as international markets [17–19]. To prevent such repercussions, adaptation tools must be promoted. To reach the strategic objective of a 50% reduction in pesticide use and risk, **integrated pest management (IPM)** must play a critical role.

Highlights

The European Green Deal demands a system-wide rethinking of Europe's approach to food production, with ambitious targets that could result in repercussions for consumers across the globe if tools for adaptation are not supported.

Integrated pest management is a holistic approach to plant health that is centered around varieties with improved biotic resistances.

New genomic techniques ease the development of varieties with durable biotic resistances through the stacking of resistance genes.

Varieties with durable biotic resistances enable a system-wide rethinking of disease control, which can result in sizable reductions of pesticide use without affecting yields.

While environmental benefits, due to the reduction in pesticide use, are to be expected from the adoption of the here reviewed cisgenic varieties, economic benefits are likely conditional on consumers' acceptance of the technology.

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Herein, we focus on a technological pillar that is broadly considered to be at the center of IPM [20], namely, the use of crop varieties with improved **biotic resistances or tolerances**. We start by briefly contrasting conventional plant breeding approaches to **cisgenesis**, which is a breeding technique that falls into the domain of **new genomic techniques** (Box 1). Subsequently, we assess mostly the potential of cisgenic potato, but also apple, varieties with stacked resistance genes toward *Phytophthora infestans* and *Venturia inaequalis*, respectively, to evaluate their contribution to the Green Deal's target of reduced use and risk of pesticides. Last, we review potential economic and environmental implications associated with this reduction in the top five EU member states with the largest production of those crops.

Plant breeding is time- and resource-demanding

Plant breeding may broadly be described by three phases [23]. First, genetic variability is generated through crossing of available elite varieties, the introduction of exotic **germplasm**, the inducement of mutations, or by using genetic engineering techniques. Second, promising recombinants or mutants are selected and tested. Last, the variety is commercialized and, ideally, adopted by farmers. The difficulty of introducing a new trait (e.g., a resistance to a certain pathogen) into a marketable variety strongly depends on the heritability of the trait and the generation time of the plant species [23]. Also, the source of the genetic variability has considerable implications for the resources needed for selecting and testing the recombinants. Often, the main time- and resource-sink that breeders face is not the process of introducing the trait of interest but rather the procedure of removing undesirable genetic material that was inadvertently inherited during the crossing of parental lines [24].

The so-called **genetic drag** describes the undesirable genetic material, which must be removed through a time and resource intensive sequence of **backcrossing** steps. The severity of the genetic drag is strongly determined by the genetic distance between the parents for the crosses, the generation time of the plant, the genetic distance between the desired gene and undesired genetically linked genes, and the availability of marker assisted selection systems, among other factors [24]. As the germplasm of wild species remains an invaluable source of biotic resistances and other agronomic traits [25–27], resources spent on removing genetic drag in conventional breeding programs are significant. Resistance genes are exchanged globally [28]. Hence, lines

Box 1. Market applications of new genomic techniques in plants

In the recent 'Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16',[ii] the European Commission defines new genomic techniques (NGTs) as techniques that are able to alter the genetic material of an organism, developed after the adoption of the EU Directive 2001/18/EC.

In 2021, the Joint Research Centre of the European Commission published two reports on the technological state-of-the-art and on current and future market applications of NGTs focusing on targeted mutagenesis [21,22]. The former report proposed a categorization of NGTs into four groups, which are distinguished on the basis of the interaction of the technique with the genome. Namely: (i) NGTs creating a double-strand break in the DNA, (ii) NGTs achieving genome editing without breaking the DNA double helix or generating only a single-strand DNA break, (iii) NGTs inducing **epigenomic** changes, and (iv) NGTs acting specifically on RNA. The latter report collected data on NGT applications and categorized the products into four stages. Namely, (i) commercial stage, (ii) precommercial stage, (iii) advanced R&D stage, and (iv) early R&D stage. In plants, 427 applications were identified with only one (soybean with a high oleic acid content) being commercialized, 16 applications were in a precommercial stage, 117 applications in an advanced R&D stage, and 292 plant applications in an early R&D stage. Applications of cisgenesis were not covered in these assessments.

In this review, the two cisgenic crops discussed were selected as case studies because : (i) both crops are currently intensively managed through pesticides, (ii) the crops are important for the European agricultural sector and cuisine, (iii) both pathogens demand the majority of the pesticide treatments in those crops, (iv) both crops are notoriously challenging to breed using conventional approaches, (v) the cisgenic varieties have been developed by European institutes, (vi) the developments are beyond a proof-of-concept with field trials supporting our evidence collection, and (vii) the technology (cisgenesis) is among the techniques that are currently under consideration in a policy initiative for a new legal framework for certain NGT plants and their food and feed products.

harboring a resistance may not be well adapted to bioclimatic conditions in other parts of the world that would benefit from the resistance; again necessitating lengthy backcrossing steps to improve the varieties' adaptation to the regional conditions.

In principle, resistance is defined as the reduction of the multiplication of the pest or pathogen, whereas tolerance defines the degree of a loss, or lack thereof, of the plants' performance under pest or pathogen pressure [29]. The genetic analysis of biotic resistance in crops dates back over 100 years [30]. Resistance or tolerance to biotic stressors may stem from a multitude of genetic factors, which can broadly be classified into **monogenic**, meaning controlled by one gene, **oligogenic**, meaning controlled by a few genes, and **polygenic**, meaning controlled by many genes with marginal contributions [5,26]. Monogenic resistances tend to be race-specific , whereas polygenic resistances are more broad spectrum [26]. This has implications for the durability of the resistance as well as for the selective pressure imposed on the pathogen population.

Many conventional breeding programs target resistances to pathogens through monogenic mechanisms [5]. The selection pressure of resistant varieties may eventually result in a reproductive advantage of natural mutations within the pathogens' genome that are able to overcome the resistance gene in the plants, which effectively limits the time of the resistance genes' efficacy [31–33]. At the same time, the pool of known resistance genes is finite. **Durable resistance** aims to address this problem and is defined as 'resistance that has remained effective during prolonged and widespread use in an environment conducive to the disease' ([34] p. 309, [35] p. 397). One approach to improve the durability of biotic resistances is through stacking several resistance genes. Stacking genes requires the pathogen to accumulate several mutations to become virulent against all resistance genes, which significantly increases the probability of a durable resistance [36–39].

Resistance to *P. infestans* and *V. inaequalis* is generally based on the recognition of a specific effector protein [32]. When recognition occurs, the hypersensitive response is initiated locally, resulting in the death of the infected cells, thus stopping the infection. Resistance genes synthesize proteins that will help to recognize pathogenic effectors [40] and are therefore a vital part of the natural plant defense mechanism.

Nowadays, agricultural value chains are highly optimized and processors as well as retailers demand increasingly specific characteristics of the harvested products to ensure that food products comply with the processing steps, quality concerns, and consumers' expectations [5]. Consequently, modern breeding programs commonly prioritize enhancing product quality, for example, the storability, juiciness, crispness, and firmness of apples [41]. Agronomic traits, such as the biotic resistances, are often seen as additional characteristics. Arguably, this may partially be related to the fact that, currently, chemical alternatives to manage pests and diseases are abundantly available in Europe (see e.g., [42] p. 195). Most benefits associated with a decreased pesticide use can be classified as public goods, whereas economic risks of this reduction are largely borne by private actors [43], which presently may result in a discrepancy between the development costs of varieties with durable biotic resistances and their market valuation. Changes in the availability of active substances due to their disapproval in the EU would increase farmers' need for alternative solutions ([44] p. 30 ff.), such as resistant varieties.

Development of cisgenic varieties

Cisgenesis (etymology: cis = same side; and genesis = origin) is an NGT and is defined as the insertion of genetic material (e.g., a gene) into a recipient organism from a donor that is sexually

Glossary

Avirulence effector: a protein detected by the plants' defense mechanism that triggers the effector-triggered immunity response and restricts proliferation of the pathogen.
Backcrossing: to cross a plant line with either of its parents.
Biotic resistances or tolerances: reduction in the multiplication of the pest or pathogen. Tolerance defines the degree of a loss, or lack thereof, of the plants' performance under pest or disease pressure.
Cisgenesis: the insertion of genetic material from a donor that is sexually compatible (crossable) without modifications/rearrangements. A cisgene contains its native introns and flanking regions identically as it appears in nature.
CRISPR/Cas: clustered regularly interspaced short palindromic repeats (CRISPR) is a family of DNA sequences. Cas is an enzyme that uses the CRISPR sequences as a guide to recognize and cleave specific strands of DNA that are complementary to the CRISPR sequence.
Durable resistance: resistance that has remained effective during prolonged and widespread use in an environment conducive to the disease.
Epigenomic: chemical changes to DNA and histones of an organism without changing the sequence of the nucleotides.
Flanking regions: DNA sequences adjacent to either side of a specific gene.
Food systems: the interconnected systems and processes that influence nutrition, food, health, community development, and agriculture.
Genetic drag: reduction in fitness (or quality) of a variety due to deleterious genes introduced along with the beneficial gene.
Germplasm: genetic material, such as plants and seeds, used by breeders for making crosses.
Integrated pest management (IPM): the consideration of all available pest control techniques and subsequent integration of appropriate measures that discourage the development of pest populations and keep pesticides and other interventions to levels that are economically justified and reduce or minimize risks to human health and the environment. IPM emphasizes the growth of a healthy crop with the least possible disruption to agro-ecosystems

compatible (crossable). The genetic material can be introduced with or without modifications/rearrangements. The former is also known as **intragenesis**. A cisgene contains its native **introns** and **flanking regions**, such as native **promoter** and **terminator** region in a sense orientation, identically as it appears in nature and conventionally bred crops [45]. Hence, cisgenic crops could in principle also be obtained by means of classical breeding, as far as the phenotype is concerned. Foreign sequences, (i.e., marker genes and vector-backbone sequence) must be absent in cisgenic crops.

Cisgenic crops can be generated by genetic transformation methods using *Agrobacterium*-mediated transformation or biolistic transformation, but without the use of selectable markers. Therefore, the selection and verification of cisgenic crops are more time consuming than a traditional gene transfer [46]. Nevertheless, because the cisgenesis approach effectively prevents genetic drag, the development time and costs of new varieties is reduced. More importantly, the approach enables the introduction of stacked resistance genes into market-ready varieties in which quality traits of the original variety remain unchanged. These advantages are particularly pronounced in plants that are vegetatively propagated and/or have long generation times, which generally complicates the (pseudo-) backcrossing steps. In general, compared with conventional breeding, NGTs may reduce the time to market by approximately two-thirds [47]. In the case of apples, the time saved may be even larger [48].

The cisgenic development steps are as follows (Figure 1, Key figure). First, relevant resistance genes need to be identified and cloned. This is a multi-year effort that requires considerable resources and often international coordination. Second, test transformations must be performed to establish optimal transformation conditions and to assess the compatibility of the cisgenes with each other and with the selected variety. Using marker-assisted selection improves the time- and cost-efficiency of this step. Third, a selection of optimal resistance gene combinations is made and a marker-free transformation of the cisgene-stack conducted. This process leads to the insertion of the desired resistance gene cassette at random positions in the genome of some cells (referred to as ‘events’). To select successful events, all regenerated shoots are tested for the presence of the inserted cisgene(s) using PCR [37,49]. Fourth, if an *Agrobacterium*-mediated transformation was used, undesired insertions of sequences, especially ones adjacent to the left and right T-DNA borders, may occur in some events (referred to as ‘backbone integration’). Therefore, whole genome sequencing must be used to select events free of backbone integration to conform to the cisgenic definition [50,51]. Fifth, the functionality of the inserted resistances is evaluated. With resistance stacks, the test of functionality is not straightforward and the response to the cognate **avirulence effector** may be used as a proxy for resistance [36]. Sixth, the stability of the resistance expression is evaluated after several rounds of clonal propagation. Last, a selection of true-to-type events is made under field conditions to ensure that other characteristics (e.g., the quality traits, and agronomic performance) of the transformed variety are unchanged [38]. For a more detailed description of the development of the two cisgenic crops reviewed here, readers are referred to Schneider *et al.* [48]. Recent scientific advances may further improve the steps described here (Box 2).

Disease management through pesticides

While in principle pesticide use varies considerably depending on agronomic, environmental, and economic conditions [63,64], the cultivation of apples and potatoes is generally accompanied by one of the most intensive fungicide regimes currently practiced in European agriculture [64–70]. Furthermore, the main targets of the majority of fungicides used in apples and potatoes are *V. inaequalis* and *P. infestans*, respectively [39,42,71–74]. Both pathogens cause disease in

and encourages natural pest control mechanisms.

Intragenesis: insertion of genetic material into a recipient organism from a donor that is sexually compatible (crossable) with the recipient organism. The genetic material is introduced with rearrangements, leading to new combinations of genetic material, such as a gene combined with a promoter from another gene.

Introns: a segment of a DNA or RNA that does not code for proteins and interrupts the sequence of genes.

Monogenic: controlled by a single gene.

New genomic technique (NGT): techniques that are able to alter the genetic material of an organism, developed after the adoption of the EU Directive 2001/18/EC.

Oligogenic: controlled by a few genes.

Pesticide: a chemical or a biological agent that deters, incapacitates, kills, or otherwise discourages pests and pathogens.

Polygenic: controlled by many genes.

Promoter: sequence of DNA where transcription initiates.

Terminator: marks the end of a gene or operon during transcription.

Treatment frequency index: calculated by dividing the total amounts of active ingredients used in each crop by the standard doses assigned to each use of the active ingredient.

Key figure

A visualization of the development steps of cisgenic varieties and an overview of the reviewed dimensions

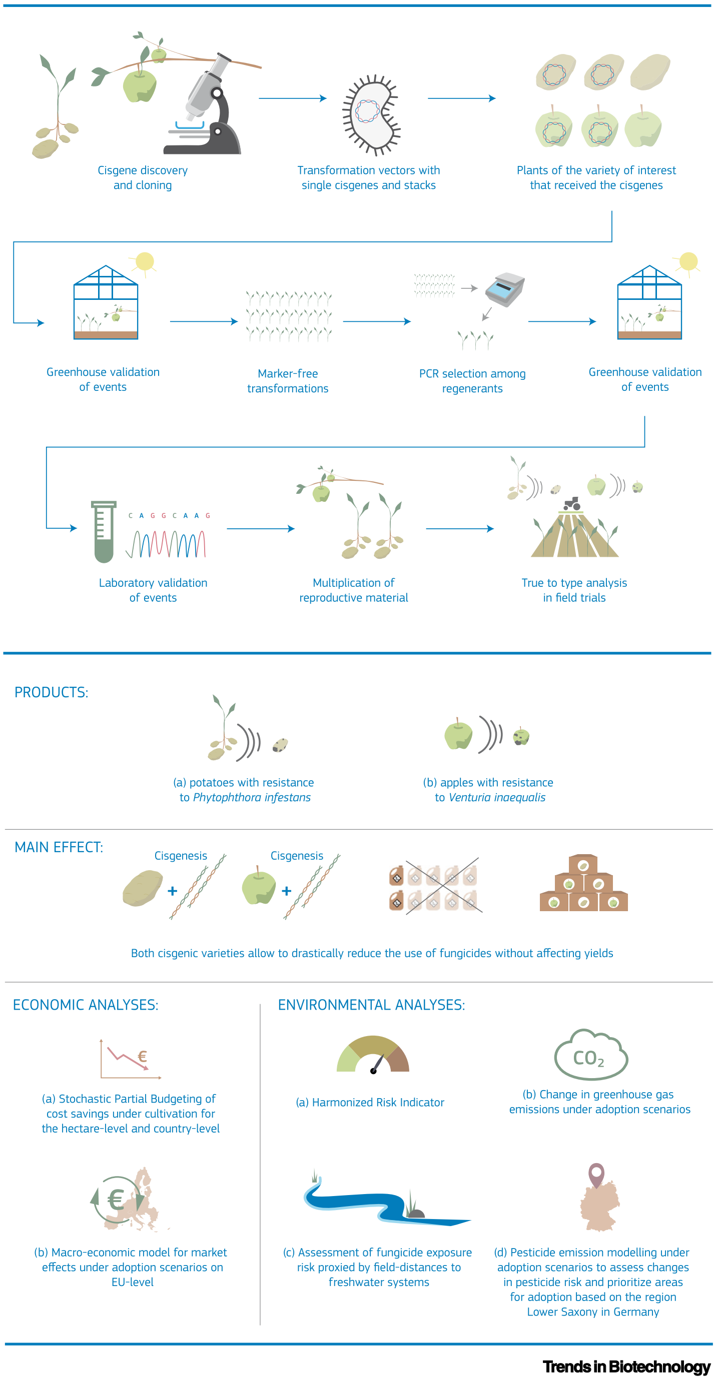

Figure 1.

Box 2. Scientific advances in developing durable resistances

Scientific advances may further improve the development of cisgenic crops, as reviewed here. For example, by increasing the development efficiency of inserting cisgenes for the resistances as well as for the selection of events [52].

Furthermore, other NGTs may be promising alternatives to the *Agrobacterium*-mediated transformation in developing cisgenic crops. For example, the **CRISPR/Cas** technique was successfully used to create cisgenic crops without any insertion of foreign sequences into the plant genome [53,54]. Notably, the DNA free CRISPR/Cas9 ribonucleoprotein delivery system was also shown to be efficient in potatoes [55].

Gene replacement and insertion by using homology-directed repair in the presence of a donor DNA is generally inefficient, mainly because the homology-directed repair occurs at much lower rates than non-homologous end-joining-mediated repair in plants. Thus, targeted insertion or replacement of long DNA sequences in plants is still challenging. Lu *et al*. [56] developed a method based on the chemically modified donor DNA for high-efficiency sequence insertion and replacement.

‘Non-host resistance’, which protects plant species from non-adapted or non-host plant pathogens, is the most common form of plant immunity. Non-host resistance arguably provides the most durable and robust form of broad-spectrum immunity against plant pathogens [57]. Witek *et al*. [58], put forward the idea, and supporting data from *Solanum americanum*, that non-host resistance may be achieved by stacking resistance genes, as described here. In line with other evidence reviewed here, potatoes with three stacked resistance genes from sexually compatible *Solanum* species showed full resistance to *P. infestans* in 3 years of Swedish field trials in the presence of complex pathogen populations [59]. Nevertheless, a promising avenue of future research to improve durable plant resistances is to knockout plant susceptibility genes using genome editing approaches [60–62]. The combination of targeted knockouts of susceptibility genes and simultaneous insertions of stacked resistance genes may achieve disease protection on a non-host level.

most of the area planted with potatoes and apples in the EU. Yet, the current adoption of varieties with resistances to these pathogens is minimal [39,42].

Consequently, both pathogens are mainly controlled through frequent, mostly preventive, fungicide applications. The Green Deal’s pesticide target may therefore pose a serious challenge. Average fungicide use data for potato production during 2012 to 2020 for growers in Germany, France, Poland, The Netherlands, and Belgium stand at 1335, 1378, 417, 1214, and 1024 tonnes of fungicides annually, respectively[iii]. Distributing the total use across the median production area suggests that fungicide use per hectare ranged from 1.4 kg in Poland, to over 5.2 kg in Germany, 7.1 kg in France, 7.5 kg in The Netherlands, up to 11.2 kg in Belgium. Similarly, the same fungicide use data for apple production suggest that growers in Poland, France, Germany, and Spain applied around 1422, 1282, 1052, and 89 tonnes of fungicides annually, respectively[iii], with a per hectare use ranging from 2.9 kg in Spain, over 8.7 kg in Poland, 25.6 kg in France, up to 31.7 kg in Germany.

With regard to the different classes of pesticides, evidence for Belgium, Germany, France, The Netherlands, and Poland consistently suggests that around 80% of all active substances used in potato fields are fungicides [65,68,70]. In most situations, *P. infestans* management requires between 10 and 20 applications of fungicides per season [72]. In terms of the kilograms of active substances used per hectare, studies report that the cultivation of potato shows the highest pesticide use in Belgium, France, and Poland compared with other arable crops [65,67,68,70]. In France, out of the 18 fungicide treatments conducted per season 14 are exclusively against *P. infestans* [70].

Treatment frequency indices for fungicides in apples ranged between 20 and 28, depending on the year, in Germany[iv]. In general, conventional producers spray their apple orchards over 20 times per season with synthetic fungicides, with French studies reporting over 30 treatments [75,76]. Organic apple producers commonly spray nonsynthetic fungicides, in particular if *V. inaequalis* susceptible varieties are grown. The strong focus on fungicide-based management of *V. inaequalis* is therefore a problem to all types of apple cropping systems [75–77].

Under experimental conditions, varieties with stacked resistance genes allowed for reductions of fungicide use by 80–90%, which corresponds to up to 23 treatments and up to 10 kg of active substances per hectare [78] (Box S1 in the supplemental information online). In what follows, we conservatively assume reductions of 50–80% to allow for treatments supporting the durability of the resistance genes (see Table S2 in the supplemental information online). No statistically significant differences in yields were observed between the cisgenic, low fungicide, IPM system, and the conventional baseline [78]. By using a resistant apple variety together with other IPM measures, the number of fungicide treatments may be reduced from 17 to 11 (35%), 25 to 22 (12%), 12 to 5 (58%), and 7 to 4 (43%), in Germany, The Netherlands, France, and Spain, respectively [79]. In other words, the expected reduction in fungicide use ranged from 12% in The Netherlands to 58% in France (see Table S2 in the supplemental information online). The latter corresponds to 15 kg of active substances less per hectare.

Economic perspectives on the adoption of cisgenic varieties

Schneider *et al.*'s [48] results suggest that the 90% confidence interval of potential cost savings per hectare from cultivating *P. infestans* resistant varieties ranged from €350 to €576 (7.8–14.7% of the total production costs) in France, €326 to €535 (6.3–11.2%) in The Netherlands, €292 to €463 (8.2–13.8%) in Belgium, €189 to €323 (5.9–10.9%) in Germany, and €49 to €99 (3.7–7.9%) in Poland (Figure 2; see Figures S1 and S2, and Box S2 in the supplemental information online). Notably, the median cost savings due to less fungicide use in resistant varieties correspond to 2.7% of the output value on a hectare in Poland, 4.2% in Germany, 4.7% in The Netherlands, 4.9% in France, and 5.7% in Belgium.

The 90% confidence interval of cost savings per hectare from cultivating *V. inaequalis* resistant varieties mirrors the large heterogeneity of farms and cost structures in the EU, ranging from €271 to €712 (2.7–8.5% of the total production costs) in France, €207 to €556 (2.4–7.3%) in Italy, €151 to €516 (1.5–5.6%) in Germany, €65 to €234 (2.3–8.7%) in Poland, and €39 to €242 (0.9–6.2%) in Spain (Figure 2; see Figures S3 and S4 in the supplemental information online). The potential cost savings due to less fungicide use in resistant varieties correspond to 1.4% of the output value in Spain, 2.4% in Italy, 2.8% in Germany, 3.1% in France, and 3.3% in Poland.

The fact that potential cost savings are small relative to the output value underlines several critical points. First, given the potential for drastic yield (quality) reductions from *P. infestans* (*V. inaequalis*) there is a lack of economic incentives to reduce chemical control. In other words, ineffective disease control in the case where resistances were overcome would easily result in monetary damages that far exceed 1–6% of revenue [39,73]. Second, there is little room for any decreases in revenues before the adoption of resistant varieties would become economically irrational for farmers. In conventional breeding, achieving breeding targets, such as the introgression of biotic resistances, is frequently accompanied by reductions in yield [5], which could outweigh the economic benefits of adopting the new variety. Under NGTs, yield drag is avoided but consumers' price discounting for products from NGT-based varieties may affect revenues [80–82]. Both factors could be problematic for the profitability-based incentive for adopting varieties with stacked resistances. However, further restrictions of the availability of active substances in the EU may result in a drastic change in farmers' demand for resistant varieties.

Cost savings at country level will strongly depend on the level of adoption of the cisgenic variety by farmers (see Figures S5–S8 in the supplemental information online). Early adopters are generally farms of larger sizes, both for new technologies in general [83–85] and genetically modified varieties in particular [86–89]. Consequently, early adoption by larger farms may result in a disproportionately larger share of the production area converted to resistant varieties.

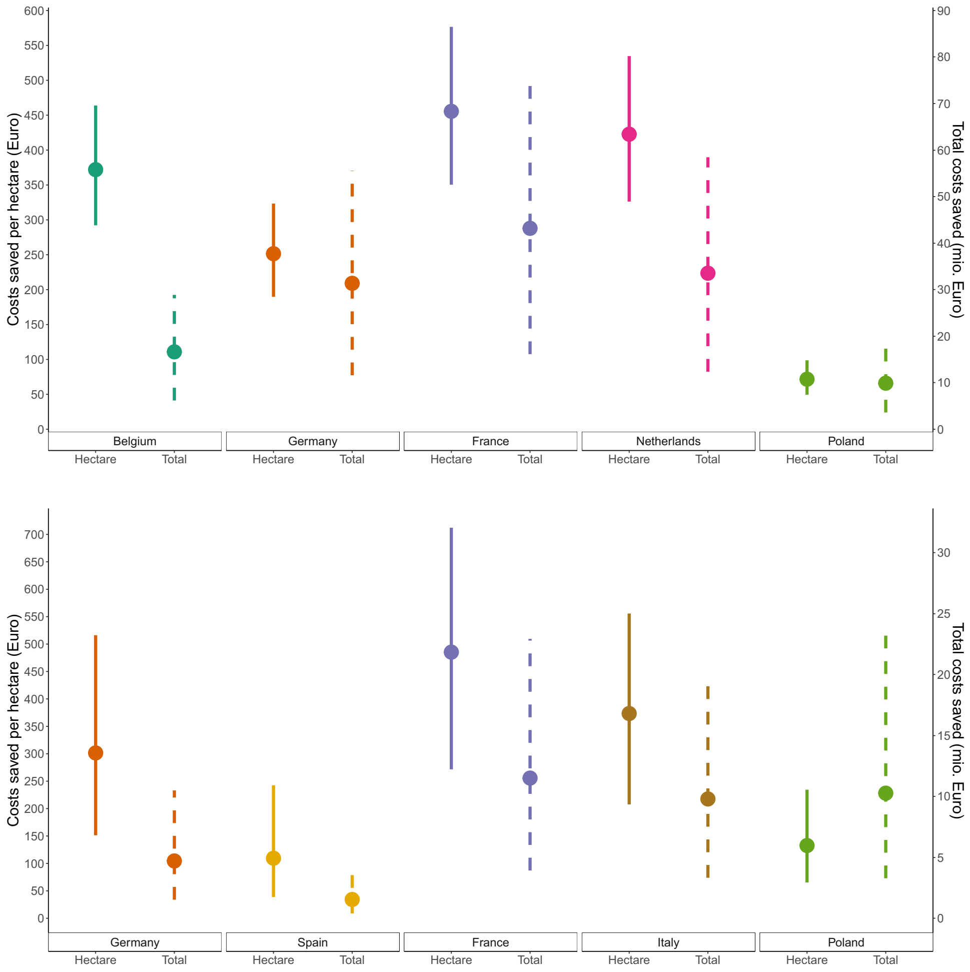

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Figure 2. The median and 90% confidence interval of the simulated per-hectare (left) and total (right) cost savings under the cultivation of *Phytophthora infestans* (top) and *Venturia inaequalis* (bottom) resistant potatoes and apples, respectively. Source: revisualized results after calculations performed in [48] using published data in conjunction with existing methods.

In the case of potato, a large share of the growing area in the five member states is cultivated by a small share of holdings (see Tables S3 and S4 in the supplemental information online). If only the largest class of potato farmers were to adopt the cisgenic potato variety, the median annual total cost savings would range from €3 million in Poland to 53 million in France (Table 1; see Figure S9 in the supplemental information online). Similarly, if only the largest farms were to adopt the cisgenic apple variety, the median annual total cost savings would range from €1 million in Spain to €9 million in France (Table 1; see Figure S10 and Table S5 in the supplemental information online).

In terms of sector-wide implications at the EU-level, using a market equilibrium model[v], Schneider *et al.* [48] simulated two adoption scenarios for the cisgenic potato variety; first, a scenario which only the largest farms adopt in the EU and reduce fungicide use by 80%, and second, a scenario which all farms adopt in the EU and reduce fungicide use by 65%. Both scenarios point to an increase of the competitiveness of potato as a crop (see Table S6 in the supplemental information online), which contrasts possible effects of the pesticide reduction under absence of varieties with

Table 1. Simulated median total cost savings at country-level, in millions of Euros, following the adoption of cisgenic varieties with durable resistances by the largest farms only[a]

Crop	Country	Holdings (%)	Area (%)	Cost savings
Potatoes	Belgium	5	24	8
Potatoes	Germany	9	71	47
Potatoes	France	11	58	53
Potatoes	The Netherlands	25	66	47
Potatoes	Poland	0.2	16	3
Apples	Germany	2.6	33	3
Apples	Spain	1.4	28	1
Apples	France	3.7	33	9
Apples	Italy	0.5	10	2
Apples	Poland	0.5	13	3

[a] Source: calculations performed in [48] using published data in conjunction with existing methods.

durable resistances [17–19]. EU supply increased between 0.98 million tonnes (2.29%) and 2.2 million tonnes (5.01%). The area cultivated with potato increased 17 thousand hectares (1.50%) to 53 thousand hectares (4.56%). The increase in supply resulted in a decline of producer prices of €8 per tonne (3.24%) to €16 per tonne (6.24%) at equilibrium. Changes to the net farm income across all agricultural activities were negligible. Potato demand increased for processing up to 984 thousand tonnes (11.6%), for human consumption up to 187 thousand tonnes (0.76%), and for feed use up to 188 thousand tonnes (3.49%). The EU imports of potatoes declined by up to 213 thousand tonnes (4.6%), whereas exports increased up to 185 thousand tonnes (6.2%). These direct market feed-backs within Europe did not capture economic gains that may arise, in particular to less developed regions, from a harmonization of the legal framework on NGTs that could ease global trade with the EU [90,91].

Cisgenic varieties contribute to environmentally friendly food systems

Schneider *et al.*'s [48] long-run projections of the adoption of cisgenic potatoes suggest that land use may shift away from other crops towards the cultivation of cisgenic potatoes. This could lead to a higher total fertilizer use, which may have implications in terms of the greenhouse gas emissions associated with fertilizer use in potatoes. However, the projections suggest that the change in greenhouse gas emissions across all agricultural activities would likely be negligible in magnitude (i.e., <0.01% of total agricultural greenhouse gas emissions; see Table S7 in the supplemental information online), underlining that the evaluated cisgenic variety would neither help nor harm the greenhouse gas emission targets if no larger system change accompanies the adoption.

The risk classification of the main substances used in fungicides in both crops suggests that the potential reduction in fungicide use could have considerable effects on the harmonized risk indicators. For *P. infestans* control in potatoes, as an example, in Germany in 2019 the five most used active substances were mancozeb, propamocarb, fluazinam, mandipropamid, difenoconazole, and cymoxanil, with more than 85% of total use. These substances belong to risk group two (three substances), group three (one), and group four (one) (see Table S8 in the supplemental information online). In the case of apples, Captan, Sulphur, Dithianon, Copper captan, sulfur, dithianon, copper hydroxide, and sulfuric lime broth jointly account for the majority of the applied quantity. These substances belong to group two (four substances) and group three (one) (see Table S9 in the supplemental information online).

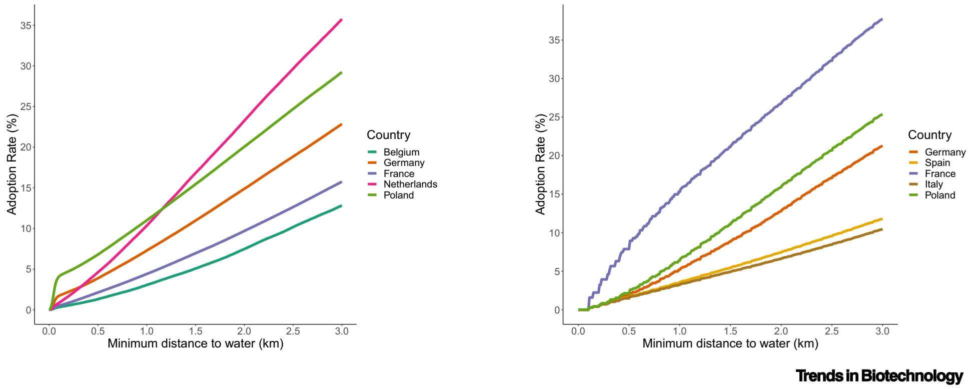

Figure 3. Hypothetical potato (left) and apple (right) adoption level, depending on the Euclidean distance to the nearest freshwater system. Computed by the share of potato and fruit pixels within a minimum distance to water. Source: calculations performed in [48] using published data ([93][vii]) in conjunction with existing methods.

The ecotoxicity of the active substances currently used is suggested to be strongly related to their presence in freshwater systems [77,92] (*c.f.* [vi]). What likely aggravates the current situation is the fact that both pressure from the fungal pathogens with the associated increase in fungicide use, as well as the abundance of freshwater systems, likely correlate with areas' precipitation levels. In other words, EU member states in which farmers currently spray fungicides more intensively, (e.g., France) are likely also the areas that have the largest number of freshwater systems in proximity to growing areas, which may be adversely impacted by a fungicide-based disease management (see Figures S11 and S12, and Tables S10 and S11 in the supplemental information online).

To proxy the exposure risk of freshwater systems in the different member states, Schneider *et al.* [48] used spatial data to compute minimum distances between potato fields and fruit orchards to different types of freshwater bodies (see Figures S13–S22 in the supplemental information online). The rationale is that the use of resistant varieties in fields closest to water systems may have increased environmental benefits. For example, converting all apple orchards less than 1 km away from any freshwater systems would correspond to 5%, 4%, 15%, 3%, and 6% of the production areas in Germany, Spain, France, Italy, and

Box 3. Scenario-based case study of fungicide risk in Lower Saxony

Schneider *et al.* [48] used the SYNOPS model together with spatially explicit information on potato fields in Lower Saxony for the period 2013 to 2018. The objective of this exercise was to emphasize the environmental heterogeneity in fungicide risk and, in turn, the heterogeneity in the benefit of adopting cisgenic potato varieties with stacked resistances. The analysis was a scenario-based assessment using the field trial fungicide data on applications in the susceptible cultivar Desiree and the here reviewed cisgenic variety for the years 2013 and 2014 in The Netherlands.

The fungicide spraying calendar in the cisgenic variety generally resulted in a reduction of fungicide risk in all categories of reference organisms. However, considerable variation of risk reduction was observed between fields and across years, due to variation in environmental conditions (Figures S23 and S24 in the supplemental information online). When farmers adhere to drift mitigation measures, the median reduction in the average risk ranged from 66-74% depending on the year considered. The median reduction for specific risk groups was 62-100% for acute aquatic risk, 75-93% for chronic aquatic risk, 78-88 % for risk to non-target organisms, and 38-58% for risk to soil organisms. If farmers do not adhere to drift reduction measures, the estimates of risk reduction are larger (see Figures S25 and S26 in the supplemental information online).

While the reduction of risk to non-target organisms appears to be evenly distributed across all fields in the region, for aquatic risks, and for risk to soil organisms especially, converting a relatively small share of the production area may already generate a majority of the environmental benefit. Depending on the annual environmental conditions, between 70% and 80% (80–95%) of the reduction in fungicide risk to soil (freshwater) organisms may be achieved by converting 15% (40%) of the area of production (see Figure S27 in the supplemental information online).

Using these 'priority cut-offs' of 15% for soil organisms and 40% for the other three risk categories, around 70% of the area of production would need to be converted to the cisgenic variety in total. Notably, between 2% and 4% of the area of production in Lower Saxony falls into the priority cut-offs in every category. These fields (red) may be the most suitable targets for adoption if the aim is to optimize the environmental benefit of earlier adopters (Figure I, and see Figures S28–S31 in the supplemental information online).

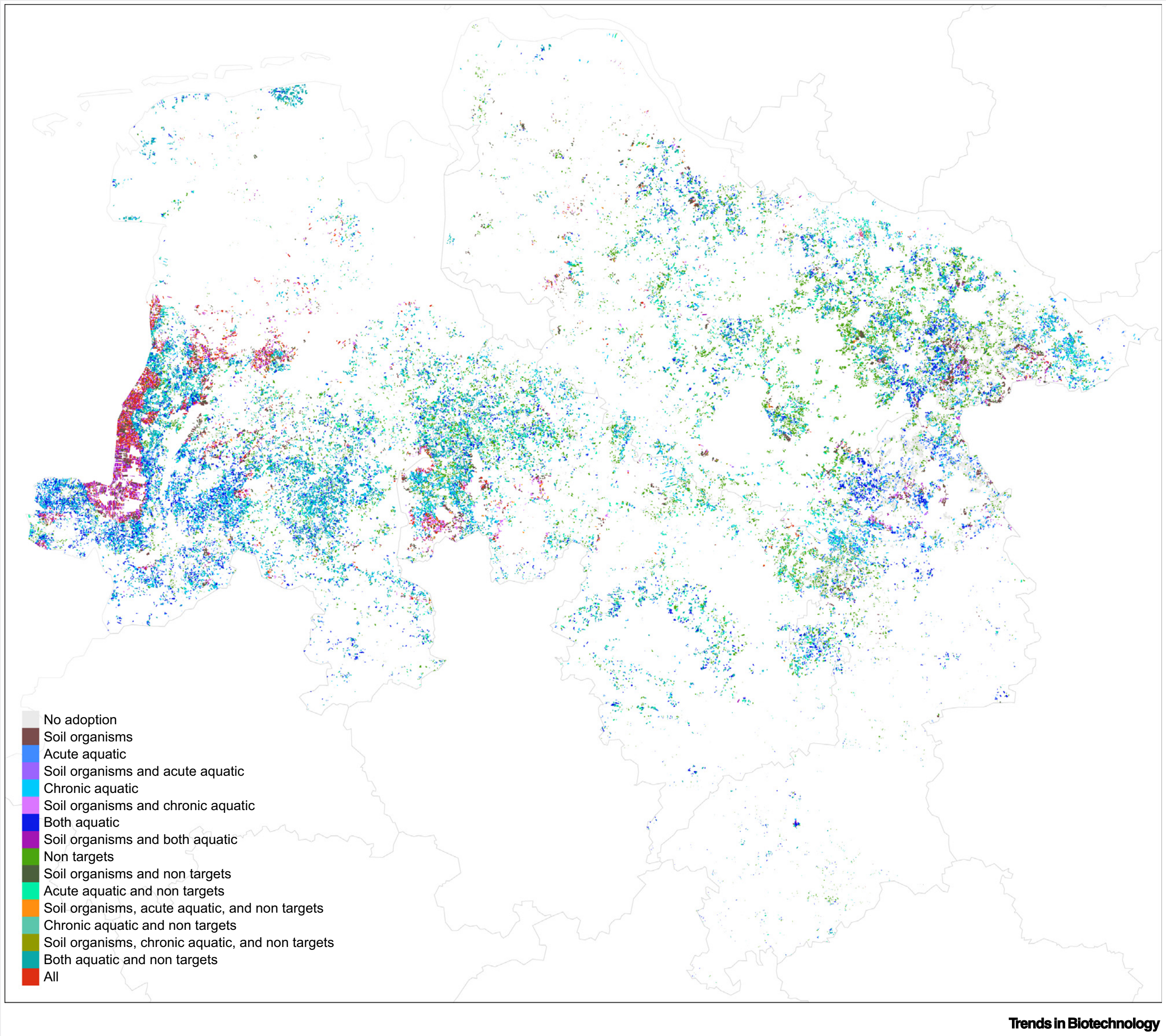

Figure I. Prioritization of fields in Lower Saxony for adoption of the cisgenic potato variety across all years for the scenario in which farmers adhere to drift mitigation measures. The coloring shows whether a field was in one or multiple priority cut-offs for the different categories of organisms benefiting from the fungicide reduction. Source: calculations performed in [48] using published data in conjunction with existing methods.

Poland, respectively (Figure 3). For potato fields in 2018, converting all fields less than 1 km away from any freshwater systems would correspond to 11%, 10%, 7%, 4%, and 3% of the production area in Poland, The Netherlands, Germany, France, and Belgium, respectively (Figure 3). Distance to freshwater may represent one aspect to consider when optimizing early adoption of the cisgenic varieties such that environmental benefits are maximized [94–96]. Potato, however, is an annual crop and cultivated in a rotation. Hence, the distance distribution may vary annually. More in-depth fungicide risk modeling was only feasible at a regional scale due to limitations in data and model availability at EU scale (Box 3).

While, broadly speaking, a societal consensus has been reached on the need to move away from pesticide-centric food systems [7,10–12], varieties developed with NGTs cannot contribute towards this without a regulatory change in the EU. In terms of environmental risks from cultivating crops developed with NGTs, scientific evidence points to no additional risks over conventionally bred equivalents [97,98]. According to the European Food Safety Authority's scientific opinion from 2022, compared with transgenesis, cisgenesis via NGTs may reduce the risks associated with unintended modifications; thus, a lesser amount of data may suffice for the risk assessment of cisgenic plants obtained through NGTs [97]. For the varieties reviewed here, various studies found no adverse effects on the environment under their cultivation [99–104].

Concluding remarks

On the one hand, the adoption of cisgenic varieties with durable resistances could provide direct economic benefits to farmers and enable crucial benefits to the environment through a lower pesticide use, thus contributing to achieving the European Green Deal target of reducing use and risk of pesticides by 50% by 2030, without risking drastic impacts to harvests and the corresponding repercussions for consumers across the world. On the other hand, the feasibility of unlocking this contribution critically depends not only on a legislative reevaluation of products obtained via NGTs, but also on the adoption rate of such varieties which, among other factors, may be driven by farmers' profitability concerns. The direct economic benefits at farm level as reviewed here assume unchanged prices. This assumption might not hold in reality, depending on the costs for, possibly mandated, traceability and labeling systems as well as the European consumers' acceptance of NGT-based products. Future work on cost-effective traceability systems, and on communication strategies that highlight the environmental benefits of certain NGT-based products to consumers, is therefore crucial (see Outstanding questions).

Outstanding questions

What are possible further biotechnological advances in the cisgenic approach to improve the development efficiency?

Which biotechnological advances could enable an efficient replacement of nonfunctional alleles in plants by functional alleles from wild relatives?

As pathogen pressure is driven by bioclimatic conditions and the optimal disease control is determined by economic characteristics, how may environmental, biological, and economic models be integrated to provide area-specific pesticide targets under the Green Deal?

What are the region-specific reduction potentials of the pesticide-induced environmental risk through the cultivation of cisgenic crops on a national and European level?

How must holistic IPM strategies be designed, both at farm- and landscape-level, to support the durability of individual and stacked resistances?

What are the environmental consequences of changes in farmers' choices of the (mix of) active substances following price responses for plant protection products due to the enforcement of the Green Deal target?

What is the most effective communication tool to enable consumers to make informed purchasing decisions of foods produced using fewer pesticides?

What would cost-effective traceability and labeling systems for NGT-based products look like?

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Declaration of interests

None are declared by the authors.

Resources

[i] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020DC0381

[ii] https://food.ec.europa.eu/plants/genetically-modified-organisms/new-techniques-biotechnology/ec-study-new-genomic-techniques_en

[iii] https://ec.europa.eu/eurostat/databrowser/view/aei_pestuse/default/table?lang=en

[iv] https://papa.julius-kuehn.de/index.php?menuid=43

[v] https://www.capri-model.org/dokuwiki/doku.php?id=start

[vi] http://sitem.herts.ac.uk/aeru/ppdb/

[vii] https://land.copernicus.eu/pan-european/corine-land-cover/clc2018

Supplemental information

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