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OPINION

New genomic techniques can contribute to reduced pesticide usage in Europe

Jens F. Sundström[1] | Anna Berlin[2] | Nam Kieu Phuong[3] | Milla Karlsson[3] | Erik Andreasson[3]

[1]Linnean Center for Plant Biology, Uppsala BioCenter, Department of Plant Biology, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden

[2]Uppsala BioCenter, Department of Forest Mycology and Plant Pathology, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden

[3]Department of Plant Protection, Swedish University of Agricultural Sciences (SLU), Lomma, Sweden

Correspondence
Jens F. Sundström, Linnean Center for Plant Biology, Uppsala BioCenter, Department of Plant Biology, Swedish University of Agricultural Sciences (SLU), SE-750 07 Uppsala, Sweden.
Email: jens.sundstrom@slu.se

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Societal Impact Statement

Can modern breeding technologies, such as genome editing, contribute to reduced pesticide usage? This question has been accentuated by a recent legal proposal to exempt genome-edited plants from the strict regulations applied to classical genetically modified (GM) crops within the European Union (EU). Using official statistics on crop cultivation and pesticide usage for two example crops commonly grown in Sweden, we calculate that cereal farmers collectively could save up to 70 million € in pesticide usage for wheat alone and that a late blight-resistant potato could reduce pesticide usage by over 80% provided that the EU legislation is amended.

Summary

The European Commission has set goals to reduce the use of chemical pesticides, and one way to meet these goals in the agricultural sector is to breed disease-resistant crops. Here, we ask whether modern breeding technologies, for example, genome editing using site-directed nucleases, can contribute to these goals. This question has been accentuated by recent legal proposals in the European Union (EU) and several other jurisdictions worldwide to exempt genome-edited plants from the strict regulations often applied to classical genetically modified (GM) crops. Using official statistics on crop cultivation and pesticide usage for two example crops commonly grown in Sweden (wheat and potato), we show that cereal farmers collectively could potentially save up to 70 million € in pesticide usage for wheat alone and that a late blight-resistant potato could reduce pesticide usage by over 80% provided that the EU legislation is amended. Given the immense potential of genome-edited crops, we further discuss details in the legal proposal currently being negotiated in the EU on the so-called new genomic techniques that includes both genome editing and targeted insertions of cisgenes. Although promising, we argue that several technical limitations in the legal proposal will, if implemented, hamper the development of disease-resistant crops and make the suggested legislation less future-proof.

KEYWORDS
European Commission, genome editing, new breeding techniques, pesticides, potato, resistance breeding, wheat

1 | INTRODUCTION

1.1 | The European Union is amending its legislation with respect to genome-edited plants

On July 5, 2023, the European Commission (EC) presented a legal proposal for a regulation concerning plants obtained by certain new genomic techniques (NGTs) (EC, 2023b). In the legal proposal, the EC suggests that plants bred using site-directed nucleases such as CRISPR/Cas9 should be classified into a new category called "New Genomic Techniques" plants. Depending on the nature and number of genetic changes that have been introduced in a NGT plant, the EC also suggests certain alleviations in the regulation of NGT plants and their food and feed compared with classical genetically modified (GM) plants that are subjected to requirements for a risk assessment, monitoring, and traceability measurements in Europe, see Directives 68/193/EEC, 1999/105/EC, 2002/53/EC, 2002/55/EC, and Regulation (EU) 2017/625. Suggested amendments to the legal proposal have just recently been passed in the European parliament (EP, 2024), and final negotiations between the three legislative entities, the EC, the EP, and the minister council are awaited shortly.

The background to the NGT legislation relates to a decision by the European Court of Justice in 2018 on plant varieties obtained using mutagenesis techniques (European-Court, 2018). In practice, the 2018 court decision ruled that all NGT plants should be regulated according to the EU genetically modified organism (GMO) legislation even though the resulting NGT varieties could be identical to conventionally bred varieties. This discrepancy put the EU legislation on GMOs at odds with several other jurisdictions worldwide (Buchholzer & Frommer, 2023) and made it practically impossible to follow the labeling and traceability regulations imposed on GM crops in Europe (ENGL, 2019). In April 2021, the EC presented a study on new genomic technologies, concluding that NGT plants could contribute to the Farm-to-Fork and Biodiversity Strategies under the EU Green Deal (EC, 2021a). The study also affirmed that the EU GMO legislation hinders the development of NGT crops in Europe (partly because of labeling and traceability requirements) and the EC concluded that the legislation is no longer "fit for purpose" and should be amended.

In the new legislation, the EC suggests that NGT plants should fall into two subcategories: category 1 NGT (NGT1) and category 2 NGT (NGT2) In short, NGT1 plants are plants in which a maximum of 20 targeted genetic changes have been introduced using site-directed nucleases, provided that the nature of genetic changes could also be obtained using conventional breeding methods, for example, random mutagenesis (EC, 2023a). In this context, genome editing is allowed, that is, point mutations, inversions, and deletions, as well as targeted insertions of cisgenes, defined as genetic elements present in the breeder's gene pool. In their proposal, the EP suggests to increase the maximum number of allowed genetic changes to account for variations in genome size and complexity between diploid and polyploid species (EP, 2024). In any case, a verified category 1 NGT plant will be considered equivalent to a conventionally bred plant and not subject to European GMO legislation. Hence, the verification process is not a risk assessment but rather an evaluation of whether the induced genetic changes also could have been obtained using conventional breeding methods. However, in contrast to conventionally bred crops, information about the breeding method must be deposited in a public database, and information on the NGT1 status must be declared in seed catalogues (EC, 2023b).

The EC also suggest that NGT plants with more than 20 targeted genetic changes or plants where the changes cannot be obtained using conventional breeding methods will fall into a separate category of NGT plants, called NGT2. Such plants will also, in the future, be regulated similarly to plants obtained using classical genetic modification techniques. In the Farm-to-Fork strategy and the EU Green deal, targets have been set to increase agricultural production and, at the same time, reduce the usage of chemical inputs, that is, pesticides (EC, 2020). The questions then arise whether NGT products could contribute to these goals and if the suggested legislative proposal, in its fine details, is permissive enough to allow for the usage of such NGT plants in European agriculture. To answer these questions, we first provide examples of NGT plants that could help reduce pesticide usage. Second, we discuss the limitations that the EC legal proposal poses on the usage of NGT plants in Europe.

2 | EXAMPLES FROM SWEDEN SHOW POTENTIAL BENEFITS OF NGT PLANTS

In 2015, in the capacity of the national competent authority, the Swedish Board of Agriculture clarified that genome-edited plants that did not contain any foreign DNA were considered equivalent to conventionally bred plants and out of the scope of the GMO legislation (Jansson, 2018). This meant that field trials of genome-edited plants could be conducted freely without any restrictions. However, the Swedish Board of Agriculture decision was overruled by the European Court of Justice in 2018 (European-Court, 2018). Still, in the few years that passed, Sweden stood out, from a European perspective, as a country where early adoption of genome-edited plants would be possible. Sweden together with a few other EU countries, that is, Belgium and Spain, has continuously had field trials of genome-edited plants despite the current GMO status (EC, 2024). Also, a public opinion study has shown that most Swedes would approve of genome-edited crops if they could be used to reduce pesticide usage

(Gentekniknämnden, 2022). In light of this positive incentive, two reports have recently been published that analyze the potential for genome-edited crops to contribute to Swedish agriculture from an economic perspective and to reduce dependence on chemical plant protection products (Jörgensen, 2023; Karlsson et al., 2023). While the examples in these reports emanate from Sweden, we think they also could be valid for other European countries should the EU decide to reform the current legislation to allow for cultivation of genome-edited crops.

3 | PESTICIDE USE IN SWEDISH CROP PRODUCTION

In Swedish agriculture, most of the pesticides are used to control weeds, with 3.2 million doses of herbicides sold in 2021, whereas the total number of hectare doses of fungicides and insecticides in 2021 was just over 1.7 million and 0.5 million doses, respectively (Kemikalieinspektionen, 2022). The largest share of plant protection products are used in cereal production, followed by sugar beet, oilseeds, and potatoes (Kemikalieinspektionen, 2022). In general, larger amounts of plant protection products are used per unit area in crops with higher economic returns, such as potatoes. Although potato crops receive many more applications than cereal crops, the area under potato is relatively small compared to cereals, and consequently the total number of fungicide doses applied is considerably higher in cereals than in potatoes (Savary et al., 2019). Thus, the total use of plant protection products in terms of doses does not reflect which crops are most affected by disease. The potential to reduce pesticide usage in absolute terms may differ between crops both due to differences in disease complexity and area under cultivation.

4 | DISEASE RESISTANCE—AN IMPORTANT BREEDING TARGET FOR SUSTAINABLE CROP PRODUCTION

All crops are more or less affected by pests and pathogens. Globally, they cause an average yield loss in crops between 10% and 30% of the potential yield (Savary et al., 2019). The level of crop loss in a particular location depends on when the infection occurs; the earlier in the crop's development, the greater the yield loss (Van der Plank, 1963). Farmers have several methods to limit the negative impact of pests and disease at their disposal that can be indirect, such as crop rotation or agronomic choices, or direct, such as pesticide treatments (Barzman et al., 2015). During the growing season, the only direct control method is the use of plant protection products. At the same time, there are several diseases where crop protection products are not efficient or are difficult to use. One such disease is Fusarium head blight that affects cereals. Chemical control of Fusarium head blight (*Fusarium graminearum*) in cereals is only possible for a short period during flowering. This makes it difficult to control the presence of harmful toxins produced by the fungi (Wegulo et al., 2015). This one of several examples to illustrate the importance of breeding for pest- and disease-resistant crops.

Traditionally, resistance breeding has been realized by crossing of different linages carrying desired traits to produce a resistant offspring (Acquaah, 2012). For this, genetic resources are found within wild relatives, old land races, and populations of plants that have been manipulated by humans to carry higher genetic diversity (Bohra et al., 2022). In recent years, technological advances such as speed breeding, next generation sequencing, and automated phenotyping platforms have greatly improved the speed and precision of the breeding process (Zaidi et al., 2020). In addition to this, the NGT tools open up new opportunities to directly target breeding efforts toward resistance against pests and plant diseases.

4.1 | Two main categories of genes are targeted in resistance breeding: R-genes and S-genes

The term resistance (R)-gene is usually applied to genes encoding immune receptors that directly or indirectly recognize pathogen effector proteins (Table 1) and initiate defense response in the plant. Most of these R-genes are dominant and encode specific (gene-for-gene) response that confer complete resistances functional in all stages of plant growth (Cook et al., 2015; Flor, 1971; Periyannan et al., 2017). The recognition of immune receptors is typically specific to a pathogen, and most often to a particular race or variant of a pathogen. When an R-gene is identified in a plant, it can often confer resistance in a similar host plant if it is incorporated into its genome (Figure 1).

TABLE 1 Aspects of R-gene and S-gene mediated resistance. The table describes the nature of R-gene- and S-gene-mediated resistance and lists the positive and negative aspects associated with either form of pathogen resistance.

	R-genes	S-genes
Description	Dominant genes that encode immune receptors and provide resistance against a pathogen.	Recessive genes that increase susceptibility to disease. Knockout mutants of S-genes increase plant resistance.
Positive aspects	Often confer complete resistance? Provides a durable resistance if combined with other R-genes	Provides a broad tolerance Stable over time, and often conserved among crops
Negative aspects	Pathogens can easily overcome resistance because it is based on single target sites. Provides a specific resistance against one pathogen	Plants are not completely tolerant.

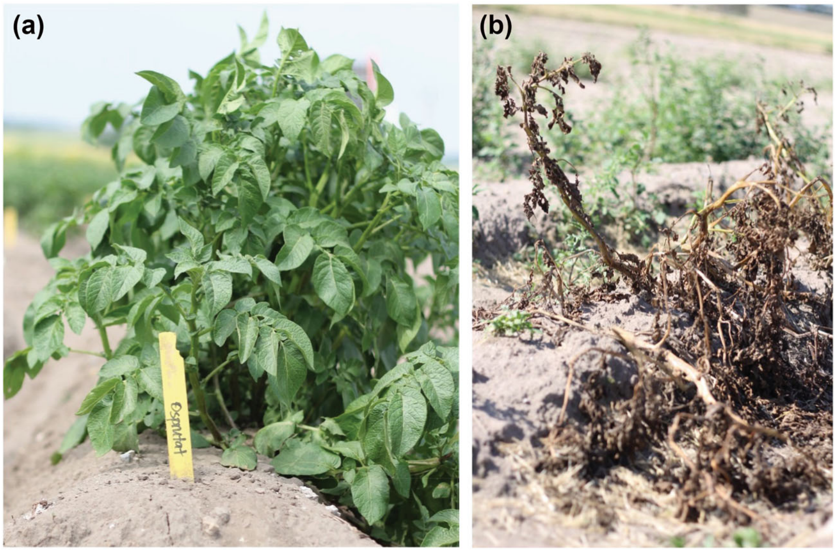

FIGURE 1 Late blight-resistant potato. The pictures show a cisgenic-resistant potato plant in (a) and a susceptible wild-type plant in (b). *Source*: Photo by Anna Lehrman.

Using R-genes in plant breeding thus harnesses a plant's natural immune system to fight disease. However, single genes in the pathogen can mutate to avoid detection by the immune receptor (Ellis et al., 2014). Thus, to achieve durable resistance, it is often necessary to combine several R-genes. This is known as pyramiding or stacking and necessitates the pathogen to mutate at multiple sites and in genes encoding different effector proteins to break the resistance and successfully infect the host (Ellis et al., 2014). A limitation to this strategy is that it is challenging to find R-genes that easily can be combined using conventional breeding methods.

Susceptibility (S) genes are genes whose function increases the susceptibility to a disease or pest infestation (Åhman et al., 2019; van Schie & Takken, 2014). They are defined by the fact that resistance is improved by knockout mutations that abolish the function of the gene. An advantage of targeting S-genes is that their knockout functions are often beneficial to different pathogens, meaning that resistance to a wide range of pests can be increased (Pavan et al., 2010) (Table 1). Often, S-gene deletion does not confer as high level of resistance as R-genes, but can still be valuable, especially for crops and diseases where R-genes are currently not available. It also helps to reduce crop losses, thus contributing to greater crop stability even in years with high disease pressure. One obstacle with S-genes is that they are recessive that means that all alleles must be mutated in order to create a disease-tolerant plant. This is challenging in conventional breeding, particularly of polyploid crops, such as wheat and potatoes. In this sense, potato is particularly complicated because it is clonally propagated and backcrossing is virtually impossible without affecting other agriculturally important traits (Acquaah, 2012). Hence, NGTs can replace conventional breeding and, in this regard, be used to mutate all alleles of an S-locus in a polyploid crop, which is often needed to achieve a broad and durable resistance (Dreiseitl, 2024; Wang et al., 2014; Zahid et al., 2024). Combining increased knowledge of S-genes with the possibility of using NGT to target mutations to all alleles of an S-locus therefore provides a promising strategy for breeding of more disease-tolerant crops.

4.2 | Resistance breeding in wheat benefits farmers

Bread wheat (*Triticum aestivum*) is a hexaploid cereal carrying three sub-genomes from three different ancestors (International Wheat Genome Sequencing Consortium [IWGSC], 2018; Martínez-Pérez et al., 1999; Wulff & Krattinger, 2022). This means that most of the genes are present in six similar but not identical variants, with two alleles from each of the three genomes. This may imply that targeted mutations in six locations are needed to knock out the function of one S-gene. Resistance breeding in wheat is further complicated by the fact that several different plant pathogens, alone or in combination, often cause disease symptoms (Figueroa et al., 2018). When breeding for disease resistance using a gene-for-gene strategy, it is therefore often necessary to introduce multiple R-genes to confer a durable resistance against the different diseases that affect wheat (Hafeez et al., 2021). In this respect, cisgenic insertions of R-genes from wild wheat species using NGTs could be a viable alternative to conventional breeding using wide crosses that often are associated with loss of critical agronomical traits.

In Sweden, approximately 450,000 ha are planted with wheat, and it is also the crop in which most of the plant protection products are used (Karlsson et al., 2023). The main diseases targeted for direct control are leaf blotch and rust disease. Without control, wheat yield losses due to diseases may range between 5% and 70% (Fisher et al., 2012; Fones & Gurr, 2015). To estimate the costs of disease, we used a moderate yield loss of 5%–10% due to these diseases (Karlsson et al., 2023). Based on the costs of control for the farmer and resulting yield reduction, the estimated loss in value for wheat is more than 70 million € annually. We note that our estimates do not consider substitution effects, and calculations of absolute economic values would require field data on the quantity and type of chemicals used, and the resulting yield. However, official statistics in Sweden are not available for that level of detail. Therefore, we base our calculations on the number of sold fungicide doses and estimates of yield losses and associated costs. These figures give a general picture of the potential to reduce pesticide usage through improved disease resistance.

In addition to the wheat pests and diseases that can be managed through the use of pesticides, a range of other pathogens with detrimental impact on wheat yields can also be managed by breeding efforts. Examples of such diseases include soil-borne fungal diseases such as sharp eyespot, caused by *Ceratorhiza cerealis* (Wu et al., 2022), and take-all disease, caused by *Gaeumannomyces tritici* (Palma-Guerrero et al., 2021). Additionally, the introduction of resistance genes against vector-transmitted viruses such as the wheat dwarf virus (WDV) (Ramsell et al., 2008) and barley yellow dwarf virus (BYDV) could potentially reduce yield losses (Aradottir & Crespo-Herrera, 2021).

4.3 | Cisgenic late blight-resistant NGT potatoes could drastically reduce pesticide usage

Most prevalent cultivars of potatoes (*Solanum tuberosum*) are autotetraploids ($2n = 4x = 48$), with a basic chromosome number of 12 (Watanabe, 2015). Autopolyploid species have multiple sets of chromosomes originating from an endogenous genome duplication. This implies that most genes are represented by four alleles in potato. Potatoes are typically propagated vegetatively through tubers (Watanabe, 2015), and conventional breeding using crosses is hampered by a high degree of inbreeding depression, high degree of allelic diversity, and difficulties with backcrossing.

In contrast to wheat, pesticide usage in Swedish potato cultivation is mainly directed toward one dominating pathogen, *Phytophthora infestans*, an oomycete that causes late blight disease. Swedish potato growers apply 223,000 ha doses of fungicides annually, of which 92% are specifically targeted toward late blight. In fact, 13% of all agricultural fungicides in Sweden are used specifically for potato cultivation, despite the fact that potatoes only occupy 0.9% of the cultivated area (Jordbruksverket, 2022b; Kemikalieinspektionen, 2022). In 2021, potatoes were grown on 23,700 ha, translating to around 8.7 ha doses of fungicide applied on each hectare against the single disease of late blight (Kemikalieinspektionen, 2022). A slightly higher actual dose per hectare can be assumed for the cultivation of table potatoes, as around 10% of table potatoes are grown organically and thus are not sprayed, and the often more resistant starch potato varieties that are sprayed with a lower frequency (Eriksson et al., 2016; Jordbruksverket, 2022a). With this number, the cost of 8.7 ha doses applied to 1 ha in 2022 would amount to 404 €, and for the total 23,410 ha of potatoes grown that year, the cost amounts to over 9.5 million € (Karlsson et al., 2023). Similar numbers have also been reported for potato cultivations in Norway, with estimated cost savings amounting to 11 million € in 2022 (Forbes et al., 2023).

It has been demonstrated that stacking three R-genes in an elite cultivar may provide a durable resistance against *P. infestans* and could significantly decrease spraying against late blight disease (Bubolz et al., 2022; Haesaert et al., 2015; Witek et al., 2016). A study of a 3-year field trial in northwestern Europe suggested that the spraying of fungicides can be reduced by 80%–90% in cultivation of resistant varieties that have been engineered using cisgenesis (Kessel et al., 2018). A reduction of 85% would lower the cost of spraying against late for an average potato grower in Sweden from 405 € per hectare to 60 € per hectare (with 2021 as the reference year). If all potato varieties grown in Sweden received stacked R-genes against late blight, the number of hectare doses against late blight could approximately be reduced from 206,000 to 31,000 (with 2021 as the reference year). The reduction would in effect lead to savings of over 8.1 million €. Similar range of savings has recently been described in other European countries (Forbes et al., 2023; Schneider et al., 2023).

Apart from late blight, potatoes are also affected by diseases caused by viruses and nematodes. However, for those diseases, chemical treatments are not a viable option. Hence, resistance breeding against viruses and nematodes may not translate into reduced pesticide usage but anyway benefit sustainable crop production. The dominating virus disease in Sweden is tuber necrotic ringspot disease, caused by potato virus Y, that can lead to around 50% yield loss (Sigvald, 2000). Yield losses caused by the nematodes *Globodera pallida* and *Globodera rostochiensis* can also be substantial in heavy infested fields (Zasada et al., 2019). A few R-genes against potato virus Y have been identified that could be introduced using NGT cisgenesis (Lacomme et al., 2017). Similarly, some resistance genes against nematodes are also available (Slootweg et al., 2017; van der Vossen et al., 2000). In addition, early blight caused by the fungus *Alternaria solani* is a problem for starch potato growers. Known R-genes are lacking for this disease, but there is a possibility to reduce the effects of *A. solani* by targeting S-genes using genome editing (Karlsson et al., 2024; Zahid et al., 2024; Zaidi et al., 2020).

4.4 | NGT use in practice—the devil is in the details

It is clear, from the examples above, that NGT plants can contribute to reduced pesticide usage but also that the required number of loci that need to be modified can be quite high, especially in polyploid species. In order to increase the longevity of—genes, the genes should be stacked, possibly combining three R-genes per pathogen. Hence, if we want to make a potato resistant against the major diseases outlined above, we would need to introduce at least nine modifications (Ghislain et al., 2019), keeping in mind that there are many more pathogens that potentially could become a disease problem in a future warmer climate. If we want to combine the use of R- and S-genes to make more generally resilient crops, the possibility to combine many target genes is of importance.

It should be noted that there are no technical limitations to the number of modifications that can be induced in a crop, and efficient methods have been developed to induce multiple mutations using one CRISPR/Cas9 construct (Yang et al., 2022). Crops also harbor inactive resistance gene homologues that could be used for gene replacement, although further research is needed to implement an effective and robust protocol for the insertion of cisgenes in plants using homologues recombination (Dong & Ronald, 2021; Han et al., 2023).

However, the EC recommends a maximum of 20 targeted mutations for category 1 NGT plants. This limit may pose a challenge for polyploid crops, such as crops like wheat or potato, particularly for recessive S-genes, where all alleles must be mutated to confer disease tolerance. In wheat, this means that if a breeder inserts mutations in three recessive traits, the plant can be classified as a category 1 NGT plant, but if a fourth gene is targeted, the resulting plant will be classified as a category 2 NGT plant and subjected to the GMO legislation. This means that we will soon hit the maximum on what can be achieved and that the limit of 20 modifications will make plant breeding in Europe less dynamic and the proposed legislation less future-proof.

According to the legal proposal, targeted insertions of DNA elements will be allowed in category 1 NGT-plants, if the inserted DNA originates from the breeder's gene pool. The term for such inserted DNA element is a *cisgene*, and the breeder's gene pool is broadly defined as genes from the same species or crossable species using breeding tools such as embryo rescue, chromosome doubling, and protoplasting. However, individual pathogens may affect different plant species that are not necessarily crossable, for example, *A. solani* and different *Fusarium* spp. strains that may cause diseases in multiple plant species. Similarly, individual resistance genes might confer resistance to a pathogen in more than one species, irrespectively if the species are crossable. For instance, late blight R-genes from potato can confer resistance in tomato and vice versa (Faino et al., 2010; Lin et al., 2022). By having a narrow definition of the breeders' gene pool, the EC restricts the number of available resistance genes, making it more challenging to build a more durable resistance. Also, the EC puts up a technical hurdle by restricting cisgenesis to targeted insertions of cisgenes. It will, according to the legal proposal, be possible to insert cisgenes in predefined genomic regions that meet a specific criteria: The insertion should not interrupt an existing gene or disturb the activity of neighboring genes. The same criteria can also be met by cisgenesis using, for example, *Agrobacterium*-mediated transformation. In fact, recent technology development allow for *Agrobacterium*-mediated insertion of cisgenes that only harbor DNA from plants (Huang et al., 2023; Rommens et al., 2005). Yet, such plants will still be regulated as GMOs because the insertion is not targeted. Hence, the demand for targeted insertion of cisgenes in category 1 NGT plants might seem like a small technical hurdle but to our judgement, it will, in fact, delay the introduction of pathogen-resistant plant varieties on the European market.

5 | CONCLUSION

The European Food Safety Authority (EFSA) has concluded that the risk profile of crop bread using NGT is comparable to that of conventionally bread crops (EFSA, 2020; EFSA, 2022), and the European Group on Ethics in Science and New Technologies has acknowledged that a one-sided prohibition of new technologies may be unethical and come with a societal cost (EC, 2021b). Here, we argue that resistance breeding using NGTs has the potential to contribute to a reduced pesticide usage in agriculture. Taking Sweden as an example, we show that cereal producers could collectively save up to 70 million € in reduced pesticide usage for wheat alone and that a late blight-resistant potato could reduce pesticide usage by over 80%.

The NGT legislative proposal holds the promise to facilitate the implementation of NGT crops in European agriculture. However, several technical limitations in the proposal will, if implemented, hamper that development. To account for differences in genome size and complexity among different plant species, we urge legislators to count the maximum number of allowed changes for a category 1 NGT plant *per basic set of chromosomes*, allowing for an increased number of modifications in polyploid species. Furthermore, to facilitate the use of R-genes, *Agrobacterium*-mediated insertions of cisgenes in regions that do not interrupt an existing gene or disturb the activity of neighboring genes should qualify as category 1 NGT plants. With these relatively small changes to the legal proposal, we think a NGT legislation will enable future-proof resistance breeding and facilitate reduced pesticide usage in Europe.

AUTHOR CONTRIBUTIONS

Jens F. Sundström, Anna Berlin, Nam Kieu Phuong, Milla Karlsson, and Erik Andreasson jointly wrote the paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Jens F. Sundström https://orcid.org/0000-0003-2848-5284
Anna Berlin https://orcid.org/0000-0002-9518-5719
Nam Kieu Phuong https://orcid.org/0000-0003-1690-6379
Milla Karlsson https://orcid.org/0000-0002-7173-2466
Erik Andreasson https://orcid.org/0000-0003-0666-7204

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