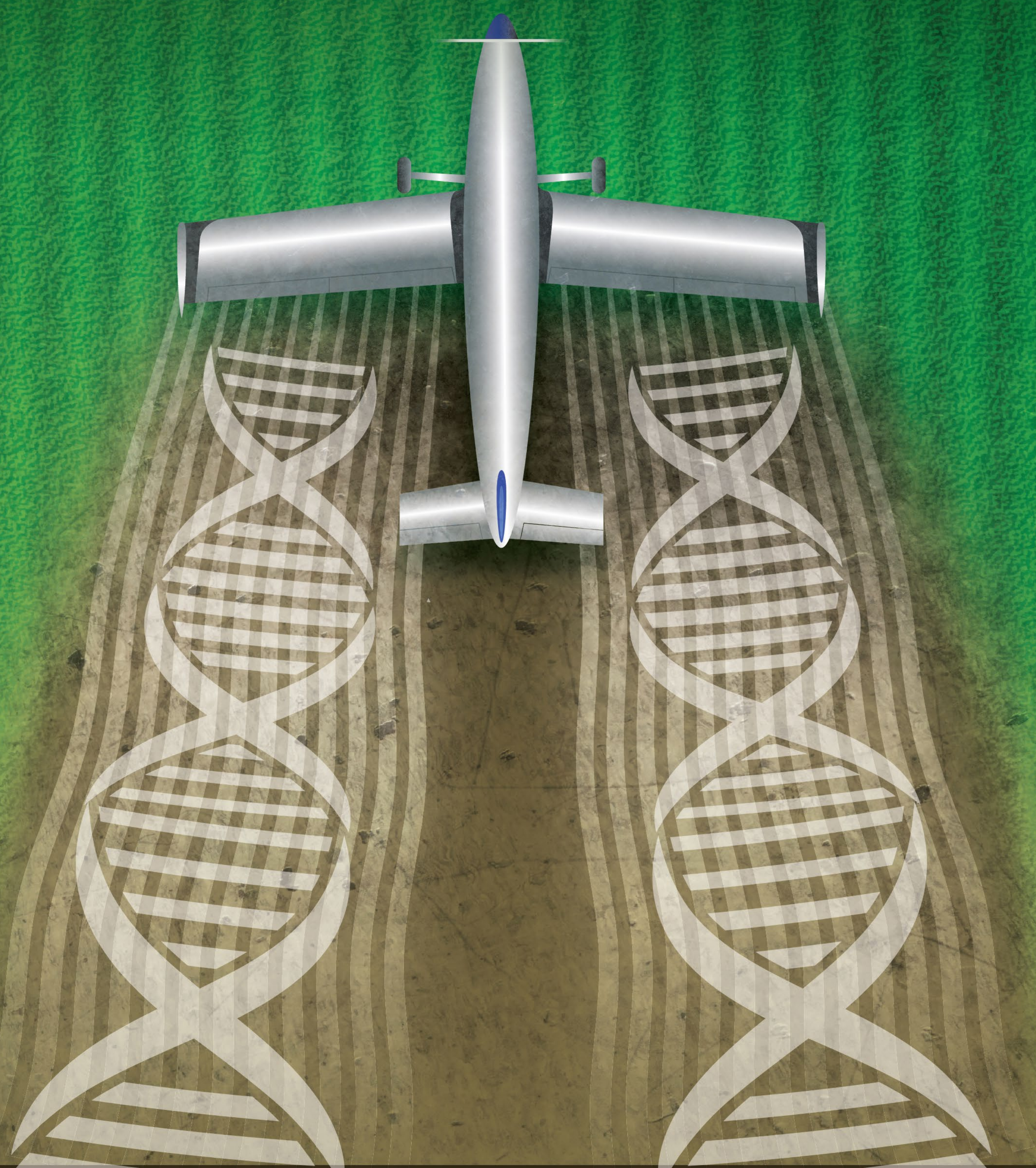
Friends of the Earth

Gene-Silencing Pesticides

Risks and Concerns



Acknowledgements

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Friends of the Earth

About Friends of the Earth:

Friends of the Earth fights to protect our environment and create a healthy and just world. We are more than one million members and activists across all 50 states working to make this vision a reality. We are part of the Friends of the Earth International Federation, a network in 74 countries working for social and environmental justice.

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Introduction

Pesticides have been linked to a range of significant unintended consequences, including harming our health, decimating biodiversity, and damaging the soil and water resources that we need to produce food now and into the future.[1] Now, the pesticide industry is developing a new wave of products using genetic engineering techniques, raising a novel set of risks and concerns.

Pesticide companies, including Bayer, BASF, and Syngenta, are developing "gene-silencing pesticides" that exploit a cellular process called RNA interference (RNAi). These pesticides are intended to switch off or "silence" genes that are essential for survival in pests, thus killing them. [i]

Rather than these technologies themselves being a genetically modified organism (GMO), gene-silencing pesticides are designed to be applied as an external product that will modify exposed organisms in the open environment. Organisms may start out their life as non-GMO and be modified partway through their life, constituting a vast, open-air genetic experiment.[2,3]

Gene-silencing RNAi pesticides would be applied to entire fields, and any exposed organism with a matching or similar gene sequence may potentially become genetically modified, whether it is a target or non-target organism.

Gene-silencing RNAi pesticides are virtually unregulated, both domestically and internationally, and therefore are on track to be commercialized without proper risk assessments or precautions. Given the enormous potential risks and major gaps in knowledge surrounding RNAi pesticides, it is imperative that civil society, farmers, and concerned scientists push for strong regulations and proper risk assessments before this technology is commercialized.

Gene-silencing RNAi pesticides constitute an open-air genetic experiment. Unintended genetic consequences could be inherited and persist in the environment for generations.

i RNA (ribonucleic acid) is a molecule essential in various biological roles in coding, decoding, regulation, and expression of genes. RNA and DNA arze nucleic acids. Along with lipids, proteins, and carbohydrates, nucleic acids constitute one of the four major macromolecules essential for all known forms of life. Some RNA molecules play an active role within cells by catalyzing biological reactions, controlling gene expression, or sensing and communicating responses to cellular signals. RNA interference is one essential regulatory process that uses certain types of "interfering" RNAs to control gene expression, by silencing or switching off genes.

How gene-silencing RNAi pesticides work

RNA interference (RNAi) is a naturally occurring cellular process in plants, fungi, and animals, including insects. The RNAi pathway controls whether a gene is turned off or not. Genetic engineers have figured out how to activate this process in organisms by using synthetic interfering RNA molecules produced in the laboratories. The resulting RNAi pesticides can kill a pest by triggering a process in the organism that turns off genes that are essential for survival.

For example, RNAi could be applied as a foliar spray on leaves. After the pest eats the leaves, interfering RNA enters the insect's stomach and silences a gene that is essential for cell division, following which the pest cannot make functioning new cells, and dies.

Gene-silencing RNAi pesticides can be applied to plants or insects directly in agricultural fields or other open-air settings via sprays, root soaks, or trunk injections.

RNAi applications could also be designed for various other functions, including as growth enhancers or as agents to reverse herbicide resistance, to modify post-harvest traits such as ripening, to initiate resistance to disease in target crops or animals, and more.

Risks, concerns, and knowledge gaps

The limitations of our knowledge and ability to predict or control the outcomes of this novel technology are profound and varied.

Environmental concerns

- **Open-air experimentation:** Genetically modifying organisms in the open environment makes controlling exposure difficult or impossible. Entire agroecosystems could be affected, and unintended genetic consequences could be inherited by plants and insects and may persist in the environment for generations.
- **Unintended silencing of genes:** RNAi technologies are widely associated with off-target activity – the silencing of genes that weren't intended to be silenced, both within the genome of target organisms as well as in related non-target species.[4,5]
- **Effects on non-target organisms, including bees and beetles:** Interfering RNA targeting a specific pest's genes may bind to and shut down genes in other organisms as well. This off-target effect may extend beyond closely related species to potentially thousands of different species.[6,7] Research already demonstrates the potential to harm beneficial insects, including honeybees[8] and beetles.[5]
- **Entrenching the pesticide treadmill:** There is evidence suggesting that, as with other pesticides, targeted pests will rapidly develop resistance to RNAi pesticides.[9,10]

Unintended consequences could include killing beneficial insects or creating public health risks.

Human health concerns

- **Inhalation of synthetic interfering RNAs:** Farmers, farmworkers, and rural communities may be exposed to synthetic interfering RNAs via spray drift. The risks pertaining to inhalation exposure are completely unknown.
- **Altering crops' genetic composition:** Unwanted gene silencing could occur in target crops as the result of exposure to RNAi pesticides. This could alter the crops' genetic composition in a way that raises safety concerns, such as altering levels of toxins or allergens.[11]
- **Dietary consumption of synthetic interfering RNAs:** Preliminary research suggests that naturally occurring interfering RNAs in our diet play a role in regulating physiological or pathological conditions in our bodies.[12,13] This suggests that synthetic RNAi products may also interfere with human gene regulation, with unforeseen health implications. Further investigation is needed to fully understand the safety implications of consuming synthetic interfering RNAs.
- **Medical research on interfering RNAs suggesting potential for toxicity:** Research investigating therapeutic uses of interfering RNAs has been hampered by the observation that they can cause an immune reaction in the body, triggering an unwanted inflammatory response.[14,15]

Socioeconomic concerns

Biotech companies are filing patents for RNAi pesticide products that include claims of property rights to exposed organisms and their offspring, regardless of whether the exposure was intentional.[16] Such patents would make owners of RNAi sprays also the owners of exposed organisms, "potentially including entire fields of conventional crops or long-lived trees and their seeds."[3] This would constitute a massive expansion of property rights over nature, ever more deeply entrenching the power of biotech and agribusiness companies over the food system, farmers and the natural world itself.

RNAi pesticide patents would constitute a massive expansion of corporate property rights over nature.

Knowledge gaps

Many significant knowledge gaps – from the genome to organism to ecosystem level—limit our ability to adequately assess the potential impacts of RNAi pesticides.

- RNAi pathways are not currently fully understood and are more complex than the simplistic, linear theory that is exploited by developers.
- It is not currently possible to predict off-target effects within organisms' genomes for a variety of reasons: target gene expression is not always static, but mediated by physiological and environmental factors, some interfering RNAs have hundreds of DNA targets, additional processes can extend the effect of the RNAi pathway across time and space once activated, and sequence-independent factors can influence off-target binding to genes.[2,17,18,19]
- It is not currently possible to design adequate bioinformatics tools that could improve our understanding of off-target effects.[17]
- We currently lack the ability to answer fundamental questions such as which species could be exposed, what their genome sequences are, or how similar the genomes of non-target organisms are to those of target organisms.
- Research conducted to date on RNAi mechanisms has primarily been in model organisms, not in the diversity of species that exist in the wild, seriously limiting our understanding of how certain species may respond to being exposed to RNAi pesticides.
- The concentration level of interfering RNAs in a product that result in a modified effect may vary between species and individual RNAs, further complicating exposure and risk assessment.

RNAi technologies are widely associated with off-target activity – the unwanted silencing of genes that weren't intended to be silenced.

Responding to industry's false claims

The biotech and agribusiness companies developing gene-silencing products are creating false distinctions between RNAi and other genetic engineering technologies and are downplaying potential risks in order to avoid regulation and achieve rapid commercialization of RNAi products.

- **Effects of RNAi pesticides are not "transient" and sometimes can be inherited across generations.** Research demonstrates that RNAi pesticides can result in heritable modifications that last up to 80 generations.[3,20] Industry patent applications for RNAi products have claimed heritability.[3]
- **RNAi pesticides are not "natural."** RNAi pesticide formulations are based on synthetically derived interfering RNA molecules. Developers may add chemicals, nanoparticles and other synthetic materials to RNAi products to enhance their function – for example, to make them degrade more slowly.
- **RNAi pesticides are not "precise."** There are significant gaps in our scientific understanding of the underlying mechanisms of the RNAi pathway, and research suggests a host of potential unintended effects from the genome to organism to ecosystem level.

Federal regulations and international guidelines

RNAi pesticide technology presents challenges for regulatory systems that were not originally designed to address the development of genetic modification agents being released into the environment. RNAi pesticides currently fall outside of existing domestic and international regulatory structures and therefore have yet to be regulated in most parts of the world.

Based on the evidence detailed in this report, RNAi pesticides should be regulated as a form of genetic engineering. RNAi processes can result in genetic changes in exposed organisms as well as altered traits that can be passed down to offspring. This has been raised by U.N. delegates at the United Nations Convention on Biological Diversity (CBD), in particular under the Cartagena Protocol on Biosafety (CPB).[21,22]

To date, country-level regulations have failed to acknowledge RNAi pesticides as a form of genetic engineering and have therefore failed to enact proper assessments or precautions for this novel technology. In the U.S. and EU, it is expected that RNAi pesticides will be regulated under existing pesticide regulations. Such regulations are inadequate to address the novel biosafety and environmental challenges of RNAi pesticides and products.

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Conclusion

Gene-silencing RNAi pesticides represent both an extension of an old, failed paradigm of pesticide-intensive agriculture, as well as a completely novel set of potential harms. Based on evidence from available scientific assessments, it is not possible to assure the safe use of RNAi products, designed to induce genetic modifications in organisms in the open environment.

The pesticide industry is pitching RNAi pesticides as a solution to a problem the industry itself created: weed and pest emergence and resistance.[23] Despite drastic and costly increases in pesticide use, some analyses show that farmers are losing more of their crops to pests today than they did in the 1940s.[24,25]

Rather than continue on a pesticide treadmill in which farmers use new formulations of toxic pesticides to deal with resistant pests, ecological farming methods offer a true solution.[26] A growing body of science shows that farmers who rely on ecological methods for pest management instead of pesticides can meet or outperform their conventional counterparts in terms of yield and profits.[27,28,29,30] Ecological farming techniques build healthy soils that confer greater pest immunity to plants and increase biodiversity in farming systems to disrupt the growth of pests and to foster natural predators. This includes crop rotations, cover cropping, composting, reducing tillage, and planting habitat for beneficial insects.

Over the past decade, a series of expert consensus reports have called for a rapid shift from input-intensive industrial agriculture to agroecological farming methods.[31,32] Business as usual is not an option. Our ability to continue to feed ourselves and future generations is at stake.

For more information and to read the full report:
foe.org/RNAI-report

Introduction

Pesticides have been linked to a range of significant unintended consequences, including harming our health, decimating biodiversity, and damaging the soil and water resources that we need to produce food now and into the future.[33] Now, the pesticide industry is developing a new wave of products using genetic engineering techniques, raising a novel set of risks and concerns.

Pesticide companies, including Bayer, BASF, and Syngenta, are developing "gene-silencing pesticides" that exploit a cellular process called RNA interference (RNAi). These pesticides are intended to switch off or "silence" genes that are essential for survival in pests, thus killing them.[ii]

Rather than these technologies themselves being a genetically modified organism (GMO), gene-silencing RNAi pesticides are designed to be applied as an external product that will modify exposed organisms in the open environment. Organisms may start out their life as non-GMO and be modified partway through their life, constituting a vast, open-air genetic experiment.[34,35] This application of genetic engineering in agriculture marks a significant departure from current applications such as genetically modified crops which can, at least in theory, be assessed in laboratories for certain unintended effects prior to cultivation and can be grown for only a single season.[iii]

Gene-silencing RNAi pesticides would be applied to entire fields, and any exposed organism with a matching or similar gene sequence may potentially become genetically modified, whether it is a target or non-target organism.

Gene-silencing pesticides constitute an open-air genetic experiment. This risks opening up a Pandora's box of unintended genetic consequences that could be inherited and persist in the environment for generations.

This technology risks opening up a Pandora's box of unintended genetic consequences that could be inherited and persist in the environment for

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iii RNAi technology is part of a growing suite of genetic engineering techniques. The most common application of genetic engineering in agriculture is insertion of foreign DNA or "transgenes" that confer herbicide tolerance in commodity crops, including corn, soy, canola, and cotton. Insertion of transgenes can also be used in conjunction with RNAi technology, whereby transgenes are inserted into crops that encode for interfering RNAs. Emerging genetic engineering techniques such as CRISPR-based genome editing are distinct from standard GMO crops and GMO crops that utilize the RNAi pathway.

generations.[iv] We must seriously interrogate the safety and efficacy of this new wave of pesticides before they are commercialized.

To that end, this report provides background on how gene-silencing pesticides work and what products are in development; details environmental, health, and socioeconomic concerns raised by these new pesticides; busts industry myths that claim these products are "precise" and "natural"; and identifies major gaps in scientific understanding and our ability to predict the consequences of applying these pesticides en masse in complex agricultural or urban ecosystems. Finally, the report summarizes how gene-silencing pesticides are virtually unregulated, both domestically and internationally, and therefore are on track to be commercialized without proper risk assessments or precautions. Such developments must be urgently challenged before yet another risky techno-fix designed to prolong flailing industrial agricultural systems is quietly unleashed onto our food and environment.

iv Concerns have also been raised by the potential for RNAi techniques to be used to create biological weapons as well as for civilian purposes, which could result in intentional or accidental harm. These uses are of particular concern because of the potential for them to evade regulation as agents of genetic modification, providing an unregulated environment for the development of novel biological weapons.[2] Alternatively, genetically modified organisms may inadvertently be created that may cause adverse effects to human health or the environment.[2]

Overview of RNAi technology

How gene-silencing RNAi pesticides work

RNA interference (RNAi) is a naturally occurring cellular process in plants, fungi, and animals, including insects. The RNAi pathway functions to control whether a gene is turned off or not. Genetic engineers have figured out how to activate this process in organisms by using synthetic molecules produced in the laboratory. The resulting RNAi pesticides can kill a pest by triggering a process in the organism that turns off genes that are essential for survival.

For example, RNAi could be applied as a foliar spray on leaves. After the pest eats the leaves, interfering RNA enters the insect's stomach and silences a gene that is essential for cell division, following which the pest cannot make functioning new cells, and dies.

Another example is an RNAi spray aimed at reversing glyphosate resistance in weeds. The interfering RNA would be absorbed by the weeds via roots or leaf penetration after which it would enter the cells of the weed and silence the gene that confers resistance to glyphosate, making the weed susceptible to glyphosate again. Such interfering RNAs could potentially be used in conjunction with glyphosate as a single-formulation product, thereby preserving the market for genetically modified herbicide-tolerant cropping systems.

There are various types of genes that developers are targeting to control insects with RNAi, namely lethal genes (essential genes that would kill the pest if disrupted), resistance/immunity-related genes (to decrease the resistance of insects to pesticides), growth/development-related genes, oviposition-related genes (to prevent parasitic pests from depositing eggs), and olfactory genes (to prevent insects from identifying crops).

RNAi pesticides interfere with gene activity in an organism. They can kill a pest by triggering a process in the organism that turns off genes that are essential for survival.

Synthetic RNAi pesticide formulations largely consist of "interfering RNA molecules" (see Box 1) as the active ingredient, along with other additional components that may enhance their efficacy – for example, nanoparticles that delay degradation in the environment or assist their penetration into cells. (See section below on concerns related to use of nanoparticles.) The formulations can have more than one active ingredient.

The formulations can be applied to plants or insects directly in agricultural fields or other open-air settings via sprays, root soaks, or trunk injections.

RNAi pesticides can reach pests in various ways depending on the organism. After being applied to a crop, they can be taken up directly via contact or ingested by the pest or pathogen. Some species, such as certain worms, are able to absorb interfering RNAs via contact,[36] while other species can ingest interfering RNAs, which are then active in the organism following digestion.[37] They can also potentially be taken up by inhalation.[2] Alternatively, the interfering RNAs can be applied to the surface of a plant, or taken up into plants either by direct leaf absorption, root uptake, or following mild abrasion of leaves or laser treatments delivered by drones. The interfering RNAs may then be transported throughout the plant and transferred to pests or pathogens that consume the plant.

RNAi pesticide formulations are designed to interact with specific gene sequences. Any exposed organism with a matching or similar gene sequence may potentially be genetically modified, whether it is a target organism or not.

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Diving deeper into RNAi pesticide mechanisms

Developers of RNAi pesticides aim to exploit naturally existing RNAi pathways in plants, animals, and fungi by manufacturing synthetic interfering RNAs of a particular sequence in order to silence a specific gene or genes. Of note, RNAi can also ultimately lead to an *increased* expression of genes.

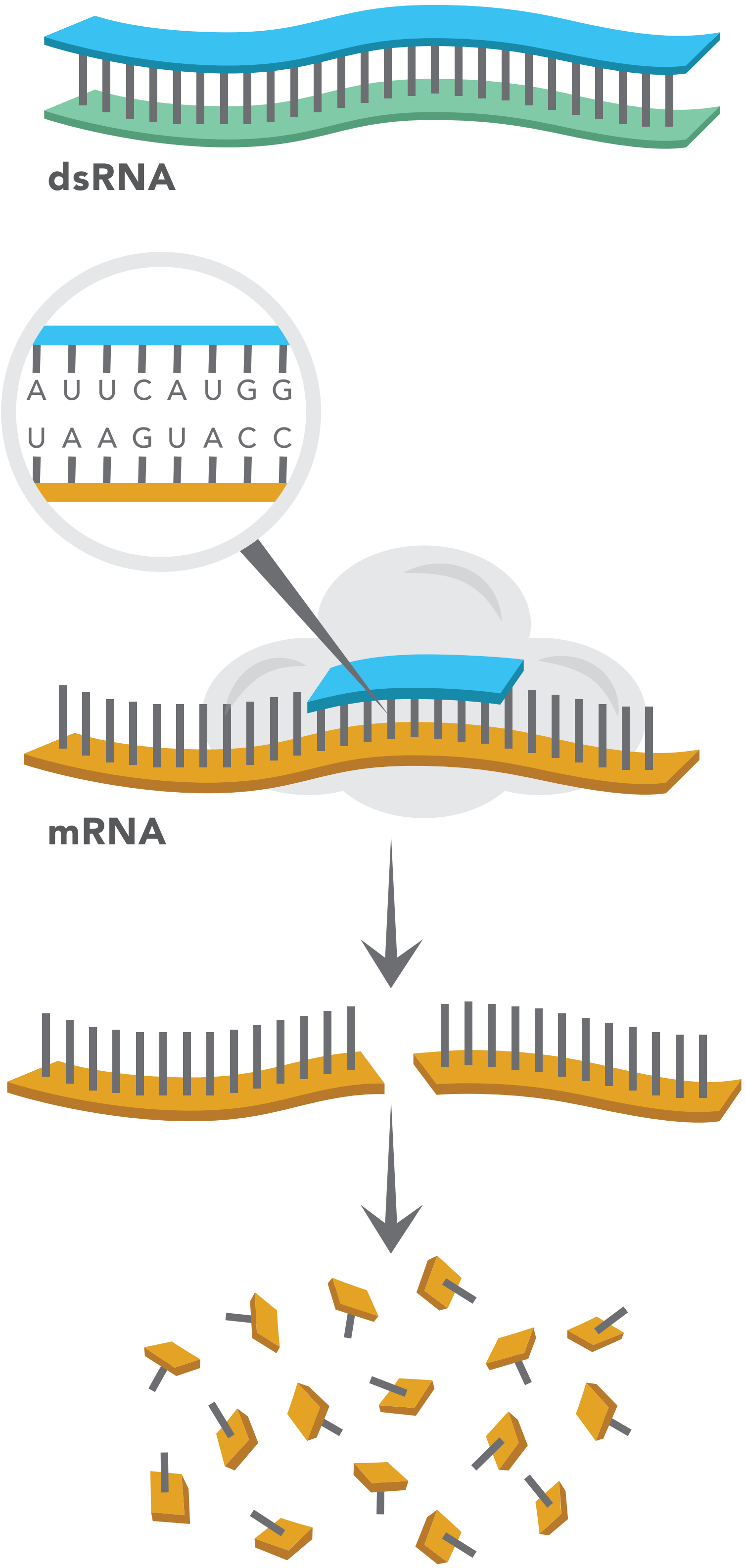
RNA interference regulates gene activity via the production of a type of RNA molecule (technically termed double-stranded RNA (dsRNA) molecules). These are dubbed “interfering RNAs” and are a type of nucleic acid molecule similar to DNA. (Similar reactions also occur in bacteria but are technically not RNAi.)

Scientists are now producing synthetic interfering RNAs that functions to turn off or “silence” genes. Silencing a gene ultimately blocks its “expression.” This may stop translation into a protein, or sometimes it stops earlier steps, a process called “transcription.” In the process of protein synthesis, genes provide the instruction codes, which involves two major steps: the transcription of the gene into messenger RNA – an intermediate molecule – and the “translation” of that messenger RNA molecule into a protein. Proteins are considered responsible for most of the cellular functions of an organism, such that altering their expression can modify traits in organisms.

RNAi functions to block production of the protein by either destroying the messenger RNA molecules, blocking their ability to be translated into proteins, or modifying the DNA so that it is not transcribed. Sometimes, these modifications are heritable.

Figure 1: The Interfering RNA Mechanism

RNAi interference functions to regulate gene expression. Interfering RNAs block protein synthesis. Proteins are the instructions for carrying out many important processes inside an organism.



Double-stranded RNA (dsRNA), dubbed 'interfering RNAs', are processed into smaller, active fragments.

The interfering RNA and a target messenger RNA bind, as they share a sequence that is matching or similar to each other.

The messenger RNA is then cleaved and destroyed. No protein is produced, resulting in 'interference' of gene expression, also known as gene-silencing.

RNAi product development

The biotech companies developing RNAi pesticides include Bayer, BASF, Syngenta, Viaqua Therapeutics, GreenLight Biosciences and others, while basic research is ongoing at universities.[38] Various RNAi products are in the pipeline for commercialization (see Figure 2). Pesticide applications include sprays, root soaks, and trunk injections. Along with pesticides, research on other topical RNAi agricultural applications is also underway, such as a spray that would reverse herbicide resistance in weeds; feed additives for fish, shrimp, and bees to initiate disease resistance; and applications to modify post-harvest traits such as ripening in order to extend shelf life of foods.

Challenges to commercialization

There are currently a number of challenges to the commercialization of these types of RNAi products. One challenge is the high cost of producing synthetic RNA, although one report asserts that costs have dropped dramatically, from approximately $600 per gram of RNA in 2017 to approximately $1 per gram in 2020[39]. Other challenges include questions around how to get RNAi molecules to move through a plant's leaves into its cells, low RNAi sensitivity in certain insect pests such as lepidopteran and dipteran pests,[40] and genetic variation that can limit their efficacy in certain populations that do not carry the genetic sequence intended for targeting. Another major challenge is the lack of stability of the RNA active ingredient once introduced into the environment — interfering RNAs are thought to break down within days. Researchers are working on various ways to make RNAi molecules more stable in the environment, including by encapsulating them in synthetic nanoparticles. (See below for health and environmental concerns related to the use of nanoparticles.)

Other applications of RNAi technology

While this report focuses on topical applications of the technology (i.e. those that would be applied externally to crops or added to feed), RNAi technology is also being used to genetically engineer crops and insects (see Box 2). The development of engineered crops is a lengthy and costly process and has a high risk of failure, spurring interest in topical RNAi products, which could potentially be developed and commercialized more quickly and which currently evade existing GMO regulations.[41]

Foliar sprays

Sprays are one of the major applications for RNAi technologies and could be used for various functions, including as pesticides, growth enhancers, agents to reverse herbicide resistance, or to initiate resistance to disease in target crops or animals.[42]

Bayer is reportedly developing various RNAi sprays which they have branded BioDirect. One is a spray designed to target glyphosate resistance in weeds.[43] This application is designed to reverse the growing problem of weed resistance to glyphosate-based

Figure 2: Key agricultural RNAi products in development

Developer	Product	Target	Stage of development
BASF We create chemistry	Spray	Plant fungal pathogen fusarium	Unclear
BAYER	Spray	Reverse glyphosate resistance in weeds	Unclear
	Spray	Canola flea beetle	Early stages
	Feed additive for honey bees	Varroa mite	Submitted for EPA registration in 2019
GreenLight BIOSCIENCES™	Spray	Colorado potato beetle	Expected to be submitted to EPA in 2020
syngenta	Spray	Colorado potato beetle	Expected commercialization within 7-10 years
DONALD DANFORTH PLANT SCIENCE CENTER	Spray	Diamondback moth	Unclear
VIAQUA THERAPEUTICS	Feed additive for shrimp	White Spot Shrimp Virus	Potential commercial launch in 2021

herbicides and, at a larger scale, to preserve the market for genetically modified herbicide-tolerant crop systems. Such interfering RNAs could potentially be used in conjunction with glyphosate as a single-formulation product. Other BioDirect products include sprays targeting the canola flea beetle (reportedly in early stages of development as of 2016).[44]

GreenLight Biosciences reportedly has a product targeting the Colorado potato that may be submitted to the U.S. EPA for registration in 2020, though there is little publicly available information on this product.[45] Syngenta also recently announced that it will have pesticides targeting the Colorado potato beetle, which are estimated to be 7-10 years away from commercialization.[46]

The Donald Danforth Center for Life Sciences and TechAccel have created a new startup called RNAissance Ag, which is also developing a spray for control of the diamondback moth.[47] The Center is looking into expanding its platform to develop similar products that target other pests, such as the fall armyworm and earworms. RNAissance Ag appear to be supplying Bayer with interfering RNAs in preliminary research publications.[48]

There are also interfering RNA topical products in development by BASF and collaborators that target the plant fungal pathogen *Fusarium graminearum*. Their 2016 research publication claims that interfering RNAs in the form of sprays were taken up by barley plants and transported to infection sites, where they were able to silence essential genes in *Fusarium*, resulting in reduced fungal growth.[49]

Root soaks and trunk injections

Insects that feed by piercing and sucking at stems or consuming root systems would not be exposed to foliar sprays that are applied to the surface of plants; therefore, companies are also developing root soaks and trunk injections as a method to deliver interfering RNAs.[50] These could be used to treat crops such as citrus trees that are slow growing and thus not ideal for transgenic strategies. There do not yet appear to be any products close to commercialization with this delivery strategy, though some patents for RNAi induction cover all potential delivery methods, including root soaking and injections.

Post-harvest food treatments

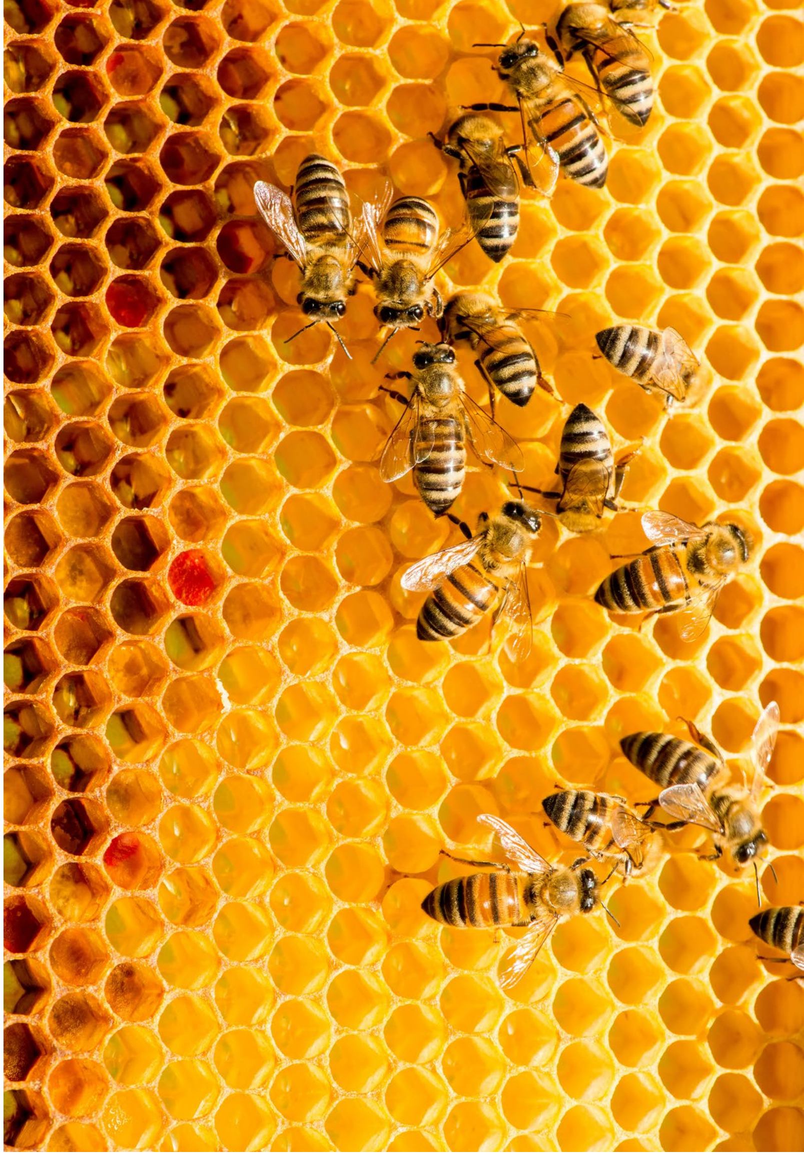
RNAi treatments for harvested crops, including fresh vegetables, fruit, grains, and flowers, are being researched as tools to prolong shelf life by tackling molds or other forms of pathogens,[2,9] or by altering genes that cause senescence – i.e., aging – in food crops.

Incorporation into feed products

Interfering RNAs are also being developed for oral delivery to farmed animals such as shellfish, small fish, and bees as a way to combat various pests and pathogens.

Viaqua Therapeutics is developing its first product designed to tackle white spot syndrome virus that affects prawn species. The company claims to have overcome issues of RNA instability in aquatic environments and feed production processes, as well as degradation in the digestive system. The latest reports suggest the company aims for commercial launch in 2021.[51]

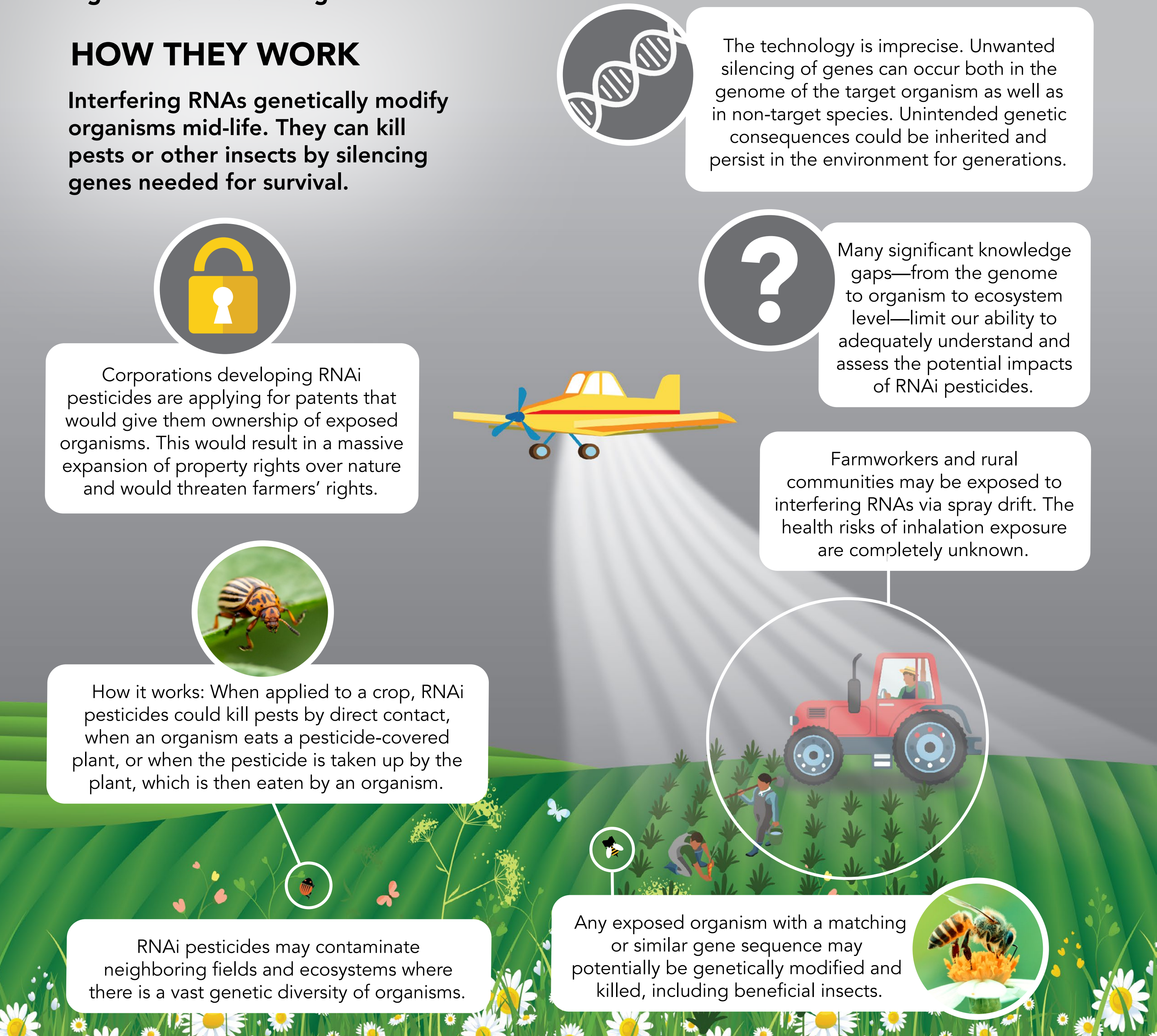
Bayer is developing a BioDirect product designed as a feed additive for honeybees to target and kill the honeybee varroa mite. However, as of 2019, Bayer stated limited success with this particular product even when combined with current mite treatments.[52] Bayer also owns Beelogics, a company that is developing RNAi feed products targeting the viral pathogen Israeli acute paralysis virus, a virus which attacks bees. Beelogics products were tested in the U.S. in 2010.[53] However, since Bayer's acquisition of Beelogics in 2012, the current status of this product is unclear.



Risks, concerns, and knowledge gaps

The limitations of our knowledge and ability to predict or control the outcomes of this novel technology are profound and varied. RNAi pathways are not currently fully understood and are more complex than the simplistic, linear theory that is exploited by developers. Researchers have already identified a range of off-target impacts both within the genome of intended organisms and in non-target organisms. Research demonstrates that unintended consequences of RNAi pesticides could include killing beneficial insects or creating public health risks for people who consume foods or who are exposed to spray drift of RNAi pesticides.

Figure 3: Gene-Silencing RNAi Pesticides



Research demonstrates that off-target impacts of RNAi pesticides could include killing beneficial insects or creating public health risks.

Environmental concerns

Open-air genetic experimentation

RNAi pesticides are intended as an in-field genetic modification technique.[2] Genetically modifying organisms in the open environment makes controlling exposure difficult or impossible. Entire agroecosystems could be affected, and unintended genetic consequences could be inherited and may persist in the environment for generations. Potential risks are amplified in the open environment where there is a vast genetic diversity of organisms and where environmental conditions may affect genetic expression in unknown ways. In fact, the majority of potentially exposed organisms are unknown, including ubiquitous beneficial bacteria and protists.[54]

Genetically modifying organisms in the open environment makes controlling exposure difficult or impossible. Entire agroecosystems could be affected, and unintended genetic consequences could be inherited and may persist in the environment for generations.

Unwanted silencing of genes

RNAi technologies are widely associated with off-target activity – the unwanted silencing of genes that weren't intended to be silenced.[55] This is not unexpected; interfering RNAs are short molecules that target only a short sequence within a gene. These short sequences may exist in multiple regions of an organism's genome. The short sequences may be found in related species as well, thus increasing the chances that gene sequences which were not meant to be affected, either in the intended recipient organisms or in non-target organisms, may be impacted in significant ways.

Effects on non-target organisms, including bees and beetles

Interfering RNAs do not have to be completely complementary to bind to a target sequence. A beneficial insect such as a pollinator may share a gene with a target pest, and even though the genes in the pest and pollinator are not identical, an interfering RNA targeting a gene in the pest may still be able to bind to and shut down a gene in the pollinator. We are limited in our ability to predict which non-target organisms may be susceptible to a given RNAi pesticide, as research shows that off-target effects may not be restricted to closely related species that share sequence similarity for a target gene.[56,57]

Even if RNAi pesticides were specific enough to silence only the intended genetic sequences, there are potentially thousands of different species in an environment that have the same sequences in their genomes which could thus have their genes silenced. What's more, the genomes of many insects aren't yet known, so scientists can't predict if their genes will match an RNA target. A 2014 scientific advisory panel convened by the U.S. EPA concluded that "knowledge gaps make it difficult to predict" exactly what problems might arise in relation to nontarget species[58].

RNAi technologies are widely associated with off-target activity – the unwanted silencing of genes that weren't intended to be silenced. Even if RNAi pesticides were specific enough to silence only the intended genetic sequences, there are potentially thousands of different species in an environment that have the same sequences in their genomes which could thus have their genes silenced.

Bees

One meta-analysis found that honeybees could be directly impacted by interfering RNAs.[59] The authors analyzed 24 studies on interfering RNAs targeting a wide range of organisms, including urban pests, parasites, pathogens, and agricultural pests. The authors found potential binding of 101 interfering RNAs to sequences of the honeybee genome. If any of those 101 interfering RNAs were released into the environment, they could potentially each activate an RNAi response in the honeybee, disrupting its gene activity, with unpredictable consequences.

Another study on bee colonies demonstrates the importance of understanding the rate of degradation of interfering RNAs and their persistence and movement through ecosystems – knowledge which is generally lacking. The 2019 study showed the uptake and exchange of interfering RNAs within bee colonies. Published by U.K.- and Israeli-based academic laboratories, the study demonstrated the uptake of interfering RNAs by worker bees, which were then horizontally transferred to jelly food and passed on to individual bees and shared across generations.[60] This horizontal spread of interfering RNAs through populations and generations highlights the potential persistence and spread of interfering RNAs. And yet, research is currently largely limited to understanding the functional roles that RNAi pathways have in organisms and populations.

Beetles

Examples of toxicity to non-target organisms can also be derived from experiences with genetically modified crops designed to produce their own interfering RNAs. A study on a genetically modified RNAi corn variety designed to kill the Western corn rootworm (by Bayer/Monsanto) found that non-target beetle species were also killed.[23] This occurred despite the genes of the non-target beetles being only 79-83% identical to that of the target pest. This shows a lack of specificity in RNAi technologies' ability to modify only the target gene in a target organism, contradicting what developers claim.[61,62]

Entrenching the pesticide treadmill

There is evidence to suggest that, as with other pesticides, targeted pests will rapidly develop resistance to RNAi pesticides. As witnessed with other transgenic strategies to date, such as insecticide- and herbicide-tolerant GMO crops, widespread resistance of weeds to glyphosate and insect resistance to Bt toxins are increasingly rendering certain genetically modified crop varieties ineffective.[63] Researchers have already documented cases of papaya ringspot viral resistance to a genetically modified papaya variety commercialized in South China that utilizes the RNAi pathway.[64] Resistance was documented in 2012, only six years after commercialization of the variety. The researchers speculated that a new viral lineage evolved in response to the RNAi mechanism.

This type of resistance is to be expected. RNAi is a major anti-viral defense mechanism, and as such, viruses have developed methods to counter it, inhibiting virtually all steps of the pathway. This results in what has been described as a "complex defence, counter-defence and counter-counter-defence arms race between host and pathogen."[65] This suggests that use of RNAi pesticides will continue to entrench the "pesticide treadmill" that is characteristic of industrial agriculture, necessitating the development of new interfering RNAs to replace older and ineffective versions. Such resistance development could serve to select for the survival of target and non-target organisms that do not possess fully functioning RNAi systems and thus render them less able to use their own natural RNAi defenses against pathogens.

There is evidence to suggest that, as with other pesticides, targeted pests will rapidly develop resistance to RNAi pesticides, further entrenching the "pesticide treadmill" that is characteristic of industrial agriculture.

Human health concerns

Inhalation of synthetic interfering RNAs

While farmers, farm workers, and rural communities may be exposed to synthetic interfering RNAs via spray drift, the risks pertaining to inhalation exposure are completely unknown. This is a serious and important knowledge gap that must be addressed.

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Altering crops' genetic composition

Unwanted gene silencing could occur in target crops as the result of exposure to RNAi pesticides. This could alter the crops' genetic composition in a way that raises safety concerns, such as altering levels of toxins or allergens. Genetic engineering processes, to date, have been shown to alter the levels of naturally existing compounds in a plant by disrupting gene activity and thus the production of proteins. For example, a recent study that undertook a molecular profile of glyphosate-tolerant "Roundup Ready" corn revealed that the activity of certain genes was increased, leading to the increased production of some compounds that are associated with human toxicity in certain contexts.[66]

Dietary consumption of synthetic interfering RNAs

Recent studies on naturally existing interfering RNAs in our diets raise questions about the safety of introducing synthetic interfering RNAs into our food system. Further investigation is needed to fully understand the safety implications of consuming synthetic interfering RNAs.

Preliminary research suggests that naturally occurring interfering RNAs in our diet play a role in regulating physiological or pathological conditions in our bodies. This suggests the possibility that synthetic RNAi products may also interfere with human gene regulation with unforeseen health implications.

And while some developers of RNAi products claim that interfering RNAs get broken down during digestion in mammals, thereby eliminating risk of any potential toxic effects,[67] research suggests otherwise. One study detected selective uptake of numerous rice interfering RNAs in different mammalian species, where it was found circulating in the blood serum of people, mice, calves, rats, horses, and sheep[5]. When the researchers investigated this further in laboratory mice, they found that one of the interfering RNAs silenced a liver gene involved in cholesterol metabolism, leading the authors to speculate whether interfering RNAs had functional significance. Another study found that not only do interfering RNAs survive mammalian digestion, they can go on to regulate mammalian genes.[68] Other studies have since confirmed the presence of naturally existing interfering RNAs in humans, including from rice, corn, barley, tomato, soybean, wheat, cabbage, grapes, and carrots.[69] Further research is needed to understand the implications of consuming interfering RNAs.

Learning from medical research on interfering RNAs

Research investigating therapeutic uses of interfering RNAs has been hampered by the observation that they can cause an immune reaction in the body, triggering an unwanted inflammatory response.[70] This is thought to be a natural cellular mechanism by which organisms can detect and combat foreign pathogens. The immunostimulatory effect can produce unwanted toxic effects, such as reduced levels of white blood cells in mammals.[71] Such effects go beyond human health risks. As noted by the U.S. EPA, it is not known how immunostimulation would affect non-target organisms, or wider food webs.[24]

Socioeconomic concerns

RNAi pesticide technology raises socioeconomic concerns, as biotech companies are filing patents for RNAi pesticide products that include claims of property rights to exposed organisms and their offspring,[72] regardless of whether the exposure was intentional.[3] As elaborated by Heinemann, such patents would make owners of RNAi sprays also the owners of exposed organisms, *"potentially including entire fields of conventional crops or long-lived trees and their seeds that have never been modified by insertion of DNA."*[3] This would constitute a massive expansion of property rights over nature, ever more deeply entrenching the power of biotech companies over the food system and the natural world itself. If RNAi pesticide products drift and contaminate untreated and off-target crops, the onus for this genetic pollution will likely fall on farmers, as we have seen with genetic contamination from genetically modified crops.[73,74] RNAi product development thus raises significant concerns for how such abuses of power may repeat themselves, threatening future farmers' livelihoods as well as agroecological farming systems that may not be able to coexist with RNAi pesticide systems.

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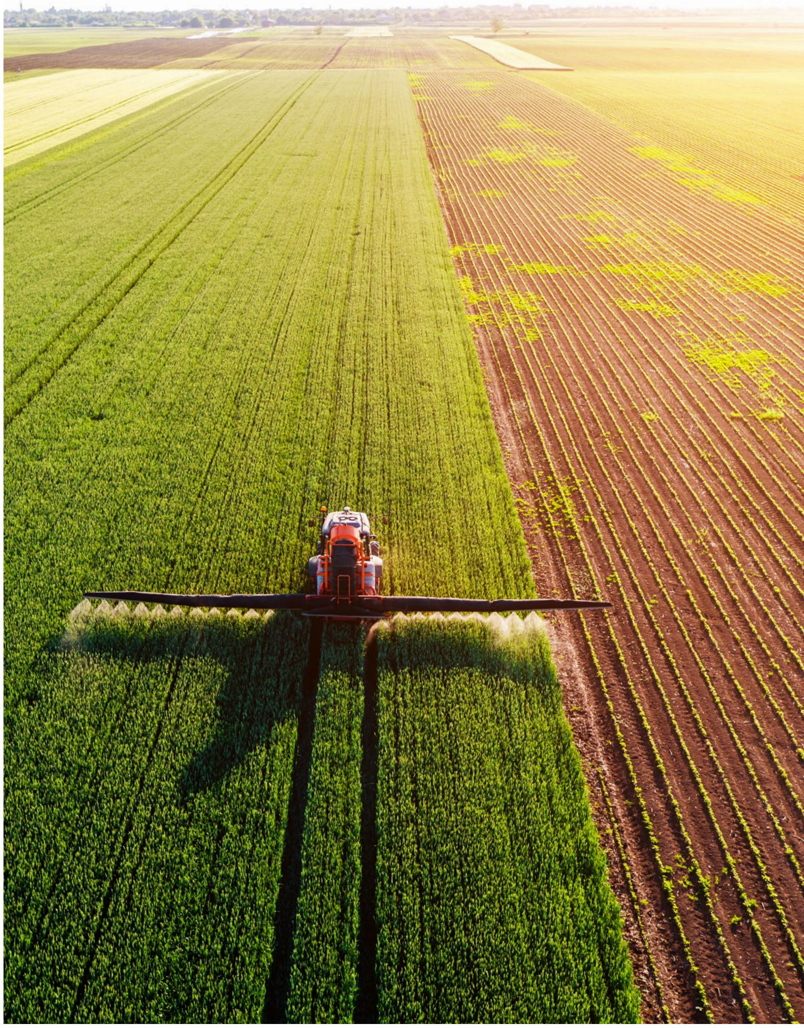
Concerns related to use of nanoparticles

Developers of RNAi pesticides make safety claims that interfering RNAs quickly degrade in the environment, thus limiting human or environmental exposure.[75] Yet developers are actively working on methods to increase the stability of RNAi sprays so that they can perform their intended function as a pesticide. Methods under development include the use of nanoparticles,[v] as certain nanoparticles have been shown to increase interfering RNA stability in the environment from 5 to 30 days and have also been shown to prevent them from being washed off of leaves.[76]

This raises both health and environmental concerns. Certain nanoparticles have been shown to cause cellular toxicity, including triggering immune responses and cell death in mammalian cells in laboratory experiments.[77] In plants, they have been shown to damage DNA, reduce nutrient uptake, and interfere with photosynthesis.[78] These significant risks have prompted scientists to call for safety evaluations before nanoparticles are used on crops.[79] Studies assessing the environmental risks of nanoparticles remain limited, although research indicates that nanoparticles may persist in surface water, groundwater, and soils.[42] The use of nano-agrochemicals has thus been described as an "intentional source of engineered nanoparticles in the environment" that may contaminate water sources and food products.[80]

In addition to these concerns, more stable interfering RNA products may lead to use across larger areas and, consequently, may increase environmental exposure in both target and non-target organisms.[2,41] However, even if "unstable," the formulations could be applied so frequently that stability is not the issue.



iv Other methods include use of genetically modified bacteria and viruses. However, these uses will likely be regulated as genetically modified microorganisms; hence, we do not cover them here.

Knowledge gaps

Many significant knowledge gaps limit our ability to adequately understand and assess the potential impacts of RNAi pesticides. It is difficult to categorize these limitations, as there are nested levels of complexity from the genome to organism to ecosystem level. We currently lack the ability to answer fundamental questions such as which species could be exposed, what their genome sequences are, or how similar the genomes of non-target organisms are to those of target organisms.

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Ideally, we would be able to model potential effects. But it is not currently possible to predict off-target effects, and it is difficult to design bioinformatics tools that could inform our understanding.[81] Which genes will be exposed to the RNAi process within a certain time and space varies, making assessment of off-target effects in laboratory conditions challenging. Analysis is also complicated by factors such as potential delays in when RNAi pathway activation occurs inside an organism and the potential for passing along the modification to future generations.[2] Further, many genes are not consistently expressed, and their expression depends on environmental context. Research conducted to date on RNAi mechanisms has primarily been in model organisms, not in the diversity of species that exist in the wild, seriously limiting our understanding of how certain species may respond to being exposed to RNAi pesticides.

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These concerns are further complicated by a number of factors. For example, some interfering RNAs have hundreds of DNA targets which are not required to have exactly the same sequence for them to be silenced. Further, once the RNAi pathway is activated in an organism by exposure to an interfering RNA, there are various additional processes that extend its effect across time and space. For example, the amplification of the interfering RNAs via the production of novel "secondary" interfering RNAs can occur in certain species (e.g., nematodes).[33] This can generate a pool of different-sized interfering RNAs and increase potential unpredictable effects on gene expression. Lastly, off-target binding to non-target genes is also influenced by sequence-independent factors such as structure and biochemical properties of the interfering RNAs, which are unique to individual interfering RNAs.[82] All of these factors, individually and combined, challenge our ability to accurately predict off-target activity.

At the ecosystem level, there are currently massive gaps in our knowledge of how many organisms may take up interfering RNAs. Depending on the form of delivery, plants other than the crop being targeted may take up interfering RNAs via the formulation (which in some cases may be as simple as water). And some organisms other than those being targeted are able to readily take up interfering RNA via direct contact, such as nematodes and arthropods, while other species appear resistant to external RNAi effects.[16] What's more, the concentration level of interfering RNAs in a product that results in a modified effect may also vary between species and individual RNAs, further complicating exposure and risk assessment.

Responding to industry's false claims

The biotech and agrichemical companies developing RNAi products are creating false distinctions between RNAi and other genetic engineering technologies and are downplaying potential risks in order to avoid regulation and achieve rapid commercialization of RNAi products.

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Effects of RNAi pesticides are not "transient" and sometimes can be inherited across generations

Developers claim that RNAi pesticides are not a form of genetic engineering but rather are "transient genetic modification." This distinction is an attempt to avoid the regulations and public rejection associated with genetically modified agricultural products. If a modification is not inherited – i.e., passed down to future generations – then proponents argue that this falls outside the definition of a GMO. The central tenet of this claim is that the effects of RNAi technologies on organisms are "transient" – in other words, temporary. However, understanding of epigenetic inheritance as well as emerging research on the heritability of RNAi alterations belies this claim. What's more, some industry patent applications for RNAi products have claimed heritability, suggesting that some developers understand that the technology can have heritable and long-lasting effects.[3]

New understandings about epigenetics demonstrate inheritance of information that is not encoded in DNA sequence. RNAi is one of the main mechanisms for such epigenetic inheritance. RNAi activity has been shown to induce heritable effects that last up to 80 generations.[3,83] A review by Heinemann (2019) summarizes the various mechanisms by which interfering RNAs can result in heritable alterations in organisms.[3] Heritable effects can be caused by inducing epigenetic changes such as chemical tagging of DNA and its associated proteins (DNA or histone modifications), which serves to turn a gene on or off. Further, interfering RNAs can be inherited via their amplification. For example, many copies of interfering RNAs are generated inside an organism following activation of the RNAi pathway or by the production of novel secondary interfering RNAs following RNAi activation, which can then be passed down to offspring. Further, long-lasting effects could also happen in long-lived organisms such as trees, when interfering RNA amplification occurs.

Interfering RNAs can also cause direct changes to the DNA in some organisms via three different mechanisms: deletions, chromosomal rearrangements, and modification of individual nucleotides. Heinemann (2019) also highlights that competition between engineered interfering RNAs introduced into an organism and endogenous interfering RNAs can lead to an imbalance of the natural levels of interfering RNA molecules.[3] This competition between interfering RNAs within an organism may thus interfere with its natural ability to tightly regulate gene activity. This could in turn have adverse effects on an organism, such as the unwanted silencing of genes that could also be passed down to future generations, or the lack of silencing of genes that should be silenced.

Such findings of long-term effects suggest that organisms exposed to synthetic interfering RNAs should be defined – and thus regulated as genetically modified organisms. And even if effects are transient, an organism exposed and modified by an RNAi spray should still fall within the definition of being "modified" and "living," as defined under the Cartagena Protocol of Biosafety.[84,85]

RNAi pesticides are not "natural"

RNAi pesticides are being described by developers as "eco-friendly" and "natural" because the active ingredient, the interfering RNA, is a form of genetic material that exists in all organisms. However, equating the safety of naturally occurring interfering RNAs in food with novel synthetically produced interfering RNAs lacks scientific grounding. Just as proteins are consumed in food, not all proteins are benign for human health. Indeed, insects also consume naturally occurring interfering RNAs on a daily basis, as it is present in the plants, animals, or fungi that form their natural diets. Nonetheless, synthetic interfering RNAs are being developed as insecticides. It is clearly dependent on the individual interfering RNAs, as with proteins, as to whether they are safe for consumption. Further, developers may add chemicals, nanoparticles and other synthetic materials to RNAi products to enhance their function – for example, to make them more resistant to degradation. They should thus be judged on a case-by-case basis and not merely assumed to be equivalent to their natural counterparts.

RNAi pesticides are not "precise"

Developers are claiming that RNAi pesticides can provide a more targeted approach than chemical pesticides, based on the concept of using interfering RNAs to target genes in a sequence-specific manner. However, as explained in detail above, current evidence reveals that those assumptions have limited scientific evidence and are false for some organisms. There are significant gaps in our scientific understanding of the underlying mechanisms of the RNAi pathway, and research suggests a host of potential unintended effects from the genome to organism to ecosystem level.

Box 2: Other applications of RNAi technology – crops and insects

While this report focuses on RNAi pesticides, which would be applied topically, it is important to understand that some companies have already used RNAi technology to develop genetically modified insects, such as mosquitoes, as well as crops, such as the Innate® potato and Arctic® apple. These RNAi crops are regulated under existing GMO regulatory structures, though concerns have repeatedly been raised about the need to improve regulations in order to address the novel and specific risks associated with RNAi-based products and applications.[86]

RNAi crops

The first genetically modified crop, the Flavr Savr Tomato commercialized in 1994, used a form of RNA-based gene silencing before it was understood to activate the RNAi pathway.[87]

More recently, corn, potatoes, apples, soybeans, and papaya using RNAi mechanisms have been commercialized. Monsanto and Dow Agroscience's SmartStax Pro (MON87411) is a line of genetically modified corn that was approved by the U.S. Environmental Protection Agency (EPA) in 2017 and approved for commodity release in several countries.[88] SmartStax Pro encodes instructions in the DNA of corn to manufacture an interfering RNA that disrupts a critical rootworm gene to kill the pest.

JR Simplot's InnateÔ potato (SPS-ØØE12-8 (E12)) was approved for cultivation in the U.S. in 2014 and subsequently for import in various countries, including Malaysia, Canada, Mexico, Japan, Australia, and New Zealand. The Innate potato carries four interfering RNA-encoding genes, three targeting acrylamide levels for "improving" frying and a fourth targeting black spot virus control.

The Arctic® apple, which targets polyphenol oxidase levels to prevent browning of the apple, was commercialized in Canada and the U.S. in 2017.[89]

Bayer, which acquired Monsanto in 2018, has commercialized a genetically modified soybean variety (MON87705), designed to alter fatty acid profiles. The company has applied for international export of this crop.

Transgenic "Rainbow" or "Sunup" papaya, developed by Cornell University and the University of Hawaii to be resistant to ringspot virus, has been commercialized in the U.S.[38] And in China, the South China Agricultural University also designed and commercialized a genetically modified papaya, called "Huanong No.1," to be resistant to ringspot virus.[38]

A cassava crop that carries a gene AMY3 (patented by Syngenta) to alter starch levels, developed in a collaboration between the International Institute of Tropical Agriculture (IITA) and the ETHZ Plant Biotechnology Lab in Zurich, has also been approved for field trials in Nigeria.[90]

In 2019, start-up company Tropical Biosciences licenced a new technology platform that uses genome editing systems to target genes that encode for interfering RNAs.[91] The aim is modifying gene expression in tropical crops, but it can also be licenced to be used for a broader range of crops such as coffee and bananas.

Various other transgenic plants using RNAi technology have also been described in the scientific literature, including those targeting traits such as nutritional enhancement, biotic stress tolerance, abiotic stress tolerance, yield and biomass enhancement, and fruit improvement.[92] However, these currently do not appear close to commercial application.

RNAi insects

Genetically modified insects have also been developed recently using RNAi technology. For example, Aedes mosquitoes have been modified to express interfering RNAs' targeting sequences within the Zika virus genome to make them resistant to infection, with the idea that they would not be able to transmit the disease to people.[93] This work also serves as a prerequisite for potential incorporation of this design into a "gene drive" version. In a gene drive, the transgenes encoding the interfering RNA molecules could be spread through mosquito populations in a "super-Mendelian" fashion (see Simoni et al. for an example of a gene drive[94]). In other words, gene drives function to skew natural inheritance patterns such that, instead of 50 percent of offspring inheriting the modification, up to 100 percent of offspring will inherit it, thus allowing for the genetic engineering of entire populations.

Research interests also include targeting mosquito genes essential for survival or disrupting mosquito functions such as olfaction and blood feeding.[95]

A company called Forrest Innovations Ltd. is developing a method to sterilize mosquitoes with interfering RNA larval treatments. The intention is to make the males sterile, with the aim of reducing overall population and thereby reducing mosquito-borne disease incidence.[96] Sterile Insect Techniques (SIT) are an old form of insect vector control where males are irradiated to make them sterile. A second product in development by the same company is the use of interfering RNA treatments to reverse pesticide resistance in mosquito populations. The treatments would be performed in the laboratory with the modified insects subsequently released into the environment. It appears that the company has yet to demonstrate any proof-of-principle data to show they can indeed induce sterility. However, in 2016 researchers from the company published a study reporting that larval treatment was able to maintain some pyrethroid pesticide sensitivity in adults.[97] However, it remains unclear when these products may be commercialized.

Federal regulations and international guidelines

Gene-silencing RNAi pesticides and other novel RNAi organisms in development currently fall largely outside of existing regulatory structures for genetically modified organisms (GMOs) and therefore have yet to be regulated in most parts of the world. This is a concerning state of affairs given the environmental and health concerns outlined above. RNAi pesticide technology presents challenges for regulatory systems that were not originally designed to address the development of genetic modification agents being released into the environment.

RNAi pesticides should be regulated as a form of genetic modification, as they can result in genetic changes in exposed organisms as well as altered traits that can be passed down to offspring.

Based on the evidence detailed in this report, RNAi pesticides should be regulated as a form of genetic engineering. Evidence demonstrates that RNAi processes can result in genetic changes in exposed organisms as well as altered traits that can be passed down to offspring – i.e., hereditary effects.

This has been raised by U.N. delegates at the United Nations Convention on Biological Diversity (CBD), in particular under the Cartagena Protocol on Biosafety (CPB). RNAi pesticides are being considered under the banner of "synthetic biological techniques" (synbio) that should be considered for regulation as a "transient modification" technology.[98] This approach recognizes the potential for such techniques to genetically modify organisms despite the product itself not being a living GMO, and thus falling outside the scope of the CBD's current GMO regulations.

Under the CBD, a genetically modified organism is defined as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology," and the CBD further defines genetic material as functioning to pass down heritable traits to offspring.[45] Additionally, the CBD ad hoc technical expert group on synthetic biology recognized "RNA interference in the form of sprays" as a "technological development" and will require specific attention by U.N. delegates at the CBD.[99] Future discussions under the CBD will need to resolve how RNAi pesticides products (or components thereof) or organisms exposed to such products and components can be assessed, safeguarded, and regulated to encompass the entirety of intended and unintended effects of such "transient modification" and synthetic biology technologies.

To date, country-level regulations have failed to acknowledge RNAi pesticides as a form of genetic engineering and have therefore failed to enact proper assessments or precautions for this novel application of the technology. Some authorities, such as New Zealand's Environmental Protection Agency, have recently placed RNAi applications outside of the scope of their GMO regulation, declaring that organisms exposed to interfering RNAs are not a form of genetic engineering.

In the U.S. and EU, it is expected that RNAi pesticides will be regulated under existing pesticide regulations, but such regulations are inadequate to address the novel biosafety and environmental challenges of RNAi pesticides and products. With this new application of genetic engineering technology, the nature of what constitutes a pesticide is changing. Pesticide regulations stop at the defined commercial ingredients of a product. This would fail to extend health or environmental assessment to any genetic changes produced inside an organism following exposure to synthetic interfering RNAs. In some cases, long "precursor" RNA molecules are used in the formulation. These precursor molecules are processed into the final active ingredient – a shorter, interfering RNA – only once it is inside an exposed organism. In such cases, most of the important final interfering RNAs that would emerge in plants, animals, or insects would not be known and therefore would not be assessed.

Even if RNAi agricultural products were regulated under the "coordinated framework" of genetic engineering policies in the U.S., health and environmental concerns would still not be adequately addressed. First, food products derived from genetic engineering are often evaluated based on GRAS (Generally Recognized as Safe) standards under the U.S. Food and Drug Administration, and therefore many of the concerns raised in this report would not be assessed. Further, the EPA requires virtually no assessment of the environmental impacts of organisms derived from genetic engineering. And the USDA's new SECURE rule (the revised federal regulation of genetically engineered organisms) institutes corporate self-governance as its standards.[100,101] In other words, industry developers may self-determine whether a genetically modified plant product should undergo regulatory review or environmental risk assessment.

With the potential risks and major gaps in knowledge surrounding RNAi pesticides, it is imperative that civil society, farmers, and concerned scientists push for strong regulations before this technology is commercialized.

Given the potential harm posed by RNAi agricultural products, they would ideally be governed by more thorough and forward-thinking regulatory oversight. Regulatory bodies should use the Precautionary Principle to guide action, meaning that precautionary measures to minimize or avoid threats to human health or the environment should be taken based on the weight of the available scientific evidence – which already indicates the likelihood of harm – rather than waiting for full scientific certainty about cause and effect, which can take years or decades. The Precautionary Principle also elevates the importance of a full evaluation of safer approaches before moving ahead with a risky new technology. Oversight should include independent assessment for public health and environmental safety, and long-term impacts should be assessed before products are released onto the market or into the environment. Decisions about RNAi pesticides and use of genetic engineering in agriculture should also incorporate societal values alongside scientific evaluation, as the impacts will be borne by society as a whole.[102] And socioeconomic concerns arising from the massive expansion of corporate patents and property rights over nature posed by this technology must be incorporated into decisions before products are commercialized.

With the potential risks and major gaps in knowledge surrounding RNAi pesticides, it is imperative that civil society, farmers, and concerned scientists push for strong regulations and proper risk assessments before this technology is commercialized.

Conclusion

It is difficult to overstate the hubris in assuming that we can safely release agents designed to induce genetic modifications in organisms in the environment without causing unintended consequences. In the development of gene-silencing RNAi pesticides, we are like the sorcerer's apprentice, with just enough knowledge to put things into motion but not enough knowledge to control the outcome. This technology represents both an extension of an old, failed paradigm of pesticide-intensive agriculture as well as a completely novel set of potential harms.

> ***This technology represents both an extension of an old, failed paradigm of pesticide-intensive agriculture as well as a completely novel set of potential harms of astonishing range. We are like the sorcerer's apprentice, with just enough knowledge to put things into motion but not enough to control the outcome.***

The pesticide industry is pitching RNAi pesticides as a solution to a problem the industry itself created: weed and pest emergence and resistance. Since the widespread introduction of synthetic pesticides after World War II, over 540 species of insects and over 360 types of weeds have developed resistance to commonly used pesticides.[103] Despite drastic and costly increases in pesticide use, some analyses show that farmers are losing more of their crops to pests today than they did in the 1940s.[104,105]

> ***The pesticide industry is pitching RNAi pesticides as a solution to a problem the industry itself created: weed and pest resistance. Rather than continue on a pesticide treadmill, ecological farming methods offer a true solution.***

Rather than continue on a pesticide treadmill in which farmers use new formulations of toxic pesticides to deal with resistant pests, ecological farming methods offer a true solution. [106] A growing body of science shows that farmers who rely on ecological methods for pest management instead of pesticides can meet or outperform their conventional counterparts in terms of yield and profits.[107,108,109,110] Ecological farming techniques build healthy soils that confer greater pest immunity to plants and increase biodiversity in farming systems to disrupt the growth of pests and to foster natural predators. This includes crop rotations, cover cropping, composting, reducing tillage, and planting habitat for beneficial insects.

Over the past decade, a series of expert consensus reports have called for a rapid shift from input-intensive industrial agriculture to agroecological farming methods.[111,112,113114] Business as usual is not an option. Our ability to continue to feed ourselves and future generations is at stake.

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