Agricultural Chemistry: New Strategies and Environmental Perspectives to Feed A Growing Global Population

A white paper examining the newest agricultural chemistry strategies for enhancing crop production and understanding their effects on the health of a growing global population and the environment in which we live.

ACS
Chemistry for Life™

Agricultural Chemistry: New Strategies and Environmental Perspectives to Feed a Growing Global Population

TABLE OF CONTENTS

ABOUT THIS REPORT

This report is for exclusive use by members of the American Chemical Society. It is not intended for sale or distribution by any persons or entities. Nor is it intended to endorse any product, process, organization, or course of action. This report is for information purposes only.

ABOUT THE AUTHOR

Christine Herman is a freelance journalist specializing in health, technology, and science reporting. Her audio work has been broadcast by Illinois Public Media and Radio Health Journal, and published online by CU-Citizen Access. She has written articles of scientific interest for Nature Chemistry, *Chemical & Engineering News* online, *inform* magazine, and Christianity Today. Christine received a master's degree in journalism and a Ph.D. in chemical biology from the University of Illinois in Urbana-Champaign.

I. Introduction

Everyone must eat to survive. That makes agricultural chemistry, arguably, one of the most broadly impactful research fields, since it has the potential to affect—for better or worse—every living person.

The United Nations predicts that a 70% increase in agricultural production will be needed to feed the estimated 9 billion people who will live on this planet in 2050.[1] As the global population grows, the great challenges that face agricultural chemists today will only become more pressing. How can more food be grown on less land? What techniques will help minimize agriculture's adverse impacts on the environment and human health? How does climate change affect agriculture, and vice versa, and what can be done about it? What role does technology have to play in the efforts to sustainably feed a growing population? And what must be done to ensure that scientific developments in agriculture receive acceptance by the general public?

This last point is especially critical in light of recent policy debates over the mandatory labeling of foods containing genetically modified organisms, or GMOs. A scientific advancement will fail to meet its highest potential if consumers reject it, thus researchers at the intersection of science and agriculture may be wise to consider what role they may have to play in public engagement.

Agriculture, which is now a $3 trillion industry,[2] has come a long way in the past several decades. The so-called Green Revolution that began in the 1940s brought about major increases in crop yields thanks to the introduction of a diverse arsenal of pesticides. Some of these chemicals were quickly found to be harmful to the environment or to human health and were eventually banned; others are still the subject of debate today. In the 1990s came the advent of genetically engineered crops, which enabled farmers, in some cases, to reduce pesticide use, better manage weeds, and grow crops in less-than-ideal conditions, among other traits. Yet the technology has also been blamed for the rise in pest resistance, and the shift toward monoculture and away from traditional farming methods and their benefits to the land.

Today, new genetically engineered plant varieties continue to be explored, and up-and-coming DNA-editing technologies may have a role to play in these developments. Biology is also lending a hand to agriculture, in the form of beneficial microbes and natural products that may help boost crop yields, ward off disease, and manage pests in a more environmentally sustainable manner. And numerous technologies are becoming inextricably linked to modern-day agriculture, such as GPS monitoring and climate modeling tools, which enable growers to tailor treatments of individual crops. The full potential of these developments remains to be discovered, and many questions are yet to be answered.

II. A Brief History of Pesticide Use in the United States

In agriculture, a pest is defined as anything that reduces the quantity or quality of the desired crop. Agricultural pests, such as weeds, insects, mites, fungi, rodents, nematodes, and plant pathogens, are managed with pesticides, a term that encompasses herbicides, insecticides, fungicides, rodenticides, and nematicides.[3]

Over the years, farmers have looked to a variety of methods for managing pests, and the options have increased as chemists and other scientists have helped expand the arsenal of pesticides. Prior to the mid-20th century, a few inorganic pesticides were available for use, but farmers primarily managed pests with cultural practices, which are non-chemical approaches to boosting yields and enhancing crop quality, and include tilling, irrigation, and selection of appropriate plant varieties for a given planting site, among other methods.

After World War II, new synthetic pesticides—including insecticide dichlorodiphenyltrichloroethane (DDT) and herbicide 2,4-Dichlorophenoxyacetic acid (2,4-D)—came onto the market and helped make crop production more efficient by increasing yields while reducing the amount of labor, fuel, and machinery required for pest management. A recent report from the U.S. Department of Agriculture (USDA) that describes trends in pesticide use from 1960 through 2008 summarizes the benefits of pesticides on agriculture.[3] Over the past half century, pesticides—together with fertilizers and improved plant varieties (from both traditional breeding and genetic engineering)—have helped increase crop yields. Corn yields rose from 20 bushels per acre on average in 1930 to more than 150 bushels per acre; in the same time span, soybean yields more than tripled, and cotton yields nearly quadrupled.

Total pesticide use has changed considerably since the 1960s. Between 1960 and 1981, pesticide use tripled on 21 crops. That accounts for nearly three-quarters of total conventional pesticide use in U.S. agriculture, an increase from roughly 200 million pounds to more than 600 million pounds. Since the 1980s, total pesticide use has trended slightly downward, to about 500 million pounds in 2008. The dramatic rise in pesticide use is largely explained by economics, as price declines made pesticides more affordable than mechanical pest management strategies that require labor, fuel, and machinery.

The types of pesticides used over the years have also changed dramatically. Early on, the pesticide market was dominated by insecticides: they accounted for nearly 60% of pesticides applied in 1960 but now account for only 6%. Herbicides have exhibited the opposite trend, jumping from less than 20% to more than 75% of pesticides applied from 1960 to 2008. In the U.S., 80% of all pesticides are applied to five crops: corn, soybeans, cotton, wheat, and potatoes, with corn in the lead, using nearly 40%. Growers and consumers alike benefit from the enhancements that pesticides provide, as crops are grown more efficiently and are made more widely available at affordable prices. But pesticide use also increases production costs for farmers—in 2008, farmers spent $12 billion on pesticides.[3]

Growers take many factors into account when making decisions about pesticides. If pest infestation levels are low and the risk of crop devastation is small, the benefits of pesticides may not justify their costs. Farmers also consider other techniques for managing pests, such as rotating crops from season to season, and mixing or alternating pesticides to decrease the chance that pests will develop resistance to the pesticides. Farmers also increasingly rely on advanced technologies, such as predictive weather models, to determine the best times for planting, spraying, and harvesting.[3] Chemical pesticides are just one tool in the arsenal for achieving good yields of a high-quality crop.

But pesticides are an important tool, nonetheless. Over the years, as more effective pesticides have been developed, farmers have been able to get away with using less, realizing both financial and environmental benefits. For example, as new chemistries in the 1980s and 1990s were developed for the creation of more effective classes of herbicides, such as sulfonylureas and imidazolinones, application rates dropped dramatically, from multiple pounds per acre to a few ounces or fractions of an ounce. Pesticide effectiveness also increased with the development of low-use-rate insecticide compounds, such as pyrethoids in the 1970s and neonicotinoids in the 1990s.[3] Pesticides also play a role in some conservation practices, such as conservation tillage, which helps reduce soil erosion compared to more intensive tillage but sometimes results in a need for increased pesticide use.

Farming strategies involving pesticides have also changed dramatically since the introduction of genetically engineered crops in the 1990s. Herbicide-tolerant crops enabled farmers to control weeds more effectively, and insect-resistant crops, which express insect-killing toxins from within, freed farmers from having to apply pesticide externally. Concern over the dangers of certain pesticides has led to changes in their use over time. Any chemical or biological agent applied to crops poses potential risks to both the environment and human health. Exposure to pesticides can be categorized as acute (such as short-term exposure of farm workers to high doses) or chronic (such as long-term exposure of crop consumers to low doses).

In 1962, marine biologist and conservationist Rachel Carson published, *Silent Spring*, a book that is credited for bringing the environmental impact of synthetic pesticides to the attention of the American public. At the time, chemical companies largely rejected Carson's reports, but her message nonetheless spurred action at the national level: DDT and other pesticides were banned or otherwise restricted in their use, and an environmental movement sprang forth, ultimately leading to the formation of the U.S. Environmental Protection Agency (EPA). The book's legacy lives on today as the chemistry community has continued to focus on more sustainable practices, both within and outside the lab.[4]

When Carson first decided to write *Silent Spring* more than half a century ago, new technologies that had been developed during World War II were being translated into commercial products, with many applications in agriculture. DDT had been used during the war to prevent the spread of disease by insects, including typhoid and malaria, and soon after the war it gained popularity on the commercial market. It was used widely—applied to fields with large-scale aerial sprayers and even applied to paint and wallpaper. Carson, as a field scientist, observed firsthand how government and industry leaders, in her view, eagerly advanced new chemicals and technologies without fully understanding the risks to human health and the environment.[4] Carson backed up her claims with scientific research, citing dozens of reports and interviews with experts. She highlighted how insecticidal chemicals can also kill the birds that feed on those insects, and can travel through the environment and the food chain, with both immediate and long-term consequences. Carson called not for an outright ban on agricultural chemicals, but rather for caution, more extensive studies, and the development of biological alternatives.[4]

And yet Carson's loudest critics were in the scientific community, the chemical industry in particular. In a review of *Silent Spring* published in the Oct. 1, 1962, issue of *Chemical & Engineering News*,[5] Dr. William J. Darby criticized Carson for failing to present the views of "responsible, broadly knowledgeable scientists" and said the book should be ignored. But instead of being ignored, Carson's ideas are credited as the catalyst for new regulations and laws that began emerging in the 1970s. In 1972, Congress called on the EPA to review the safety of pesticides, and the agency subsequently concluded that some pesticides, including DDT, aldrin, dieldrin, chlordane, and heptachlor, posed unreasonable risks. The registrations for these pesticides were canceled, suspending their sale, distribution, and use. A couple of decades later, additional compounds faced scrutiny. In the 1990s, some or all uses of the organophosphates ethyl parathion and mevinphos were cancelled following reports of farm workers developing exposure-related illnesses from them. Since 2000, insecticides based on carbamates and organophosphates have declined, while pesticides with less acute toxicity to humans, such as pyrethoids and neonicotinoids, have increased. Around the same time, when genetically modified crops expressing the insect-killing protein derived from the bacterium *Bacillus thuringiensis* (and referred to as the "Bt toxin") gained popularity, synthetic insecticides—including both acutely and chronically toxic varieties—dropped in use.[3]

Much of the regulatory action taken against pesticides over the years has focused on chemicals with high acute toxicities. But some compounds with low acute toxicities have come into the spotlight as evidence surfaced of risks caused by chronic exposure to them. For example, when the growth regulator daminozide, which had been used on apples, was found to have a dietary carcinogenic risk, an EPA review resulted in voluntary cancellation of all uses on food crops in 1989. From the 1980s into the mid-2000s, two EPA reviews of ethylene-bis-dithiocarbamate-based fungicides, which had raised concerns about carcinogenic, developmental, and thyroid effects, led to cancellations of registrations for food use and other restrictions for reducing risks to both humans and some aquatic and terrestrial animals.[3]

In the 1980s and 1990s, scrutiny over several different herbicides implicated as carcinogens, including triazines and acetanilides, resulted in restrictions that encouraged changes in their use and monitoring of their levels in drinking water. The adoption of genetically modified crops with resistance to the herbicide glyphosate also led to a reduction in the use of triazines and acetanilides, with a concurrent increase in the use of glyphosate, which now accounts for roughly 50% of total herbicide use and has low acute toxicity.[3] Although glyphosate has generally been considered more environmentally benign than other pesticides, a 2015 report from the cancer arm of the World Health Organization (WHO)—the International Agency for Research on Cancer (IARC)—stated that glyphosate, which is sold by biotech firm Monsanto as Roundup, is "probably carcinogenic to humans," namely linked to non-Hodgkin's lymphoma.[6] The assessment was based on evaluation of evidence of human exposures in the U.S., Canada, and Sweden published since 2001. But Monsanto is urging the WHO and regulatory agencies to reexamine the evidence cited in the report, arguing that IARC ignored some of the most relevant data.

One of the most widely discussed pest management issues today is the development of resistance to pesticides—in particular, the development of glyphosate-resistant weeds and the Bt toxin-resistant worm populations. Widespread use of any pesticide gives pests the opportunity to evolve mechanisms that enable them to survive exposure. When resistance develops, growers often incorporate the use of additional pesticides that may be more toxic to mammals. It's an endless cycle, because resistance can potentially be developed to any pesticide if it is used for a long enough time, but there are both chemical and non-chemical methods to combat the problem.

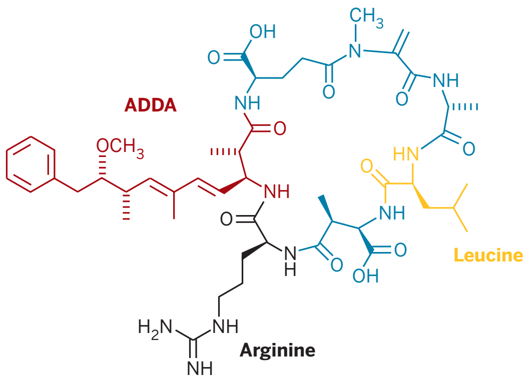
III. Fertilizers: The Cost of Adding Nutrients to Boost Crop Yields

While pesticides combat the myriad pests that can destroy a crop, fertilizers help boost yields by either adding nutrients to the soil or enhancing the soil's ability to retain water or remain aerated. Most fertilizers provide plants with a combination of macronutrients (such as nitrogen, phosphorus, potassium, calcium, magnesium, or sulfur) and micronutrients (including copper, iron, manganese, molybdenum, zinc, and boron).[7]

Nitrogen is the most important nutrient for plant growth, as it is present in proteins, DNA, chlorophyll, and other components. DNA, ATP, and some plant cell lipids require phosphate, making it another critical nutrient. Although the atmosphere is full of nitrogen, most organisms, including plants, are unable to break apart the triple bond between nitrogen atoms. So plant health is dependent on a form of nitrogen termed "fixed nitrogen," which encompasses ammonia, ammonium ions, nitrate, or nitrogen oxide. Natural nitrogen fixation can be performed by certain strains of bacteria known as diazotrophs, including some that live in the root systems of plants.[7] Fixed nitrogen can also be formed when lightning strikes the earth, providing the energy needed to react nitrogen gas with water to yield nitrates and ammonia.

Over the years, scientists have created methods for fixing nitrogen synthetically. The first method ever developed is known as the electric arc process, devised by Lord Rayleigh in 1895, and is essentially a re-creation of a lightning strike in the lab. Then, in the early 1900s, the Haber-Bosch process gained popularity—the technique uses an iron catalyst to react nitrogen with hydrogen to form ammonia. Finally, the cyanamide process was developed to convert calcium carbide and nitrogen into calcium cyanamide. Fixed nitrogen is also found in abundance in crop waste and fecal matter, which is why waste from animals, including humans, has been used on fields to return nitrogen to the soil for millennia.
But the agricultural boost achieved with fertilizers does not come without a cost. For one, nitrates are explosive compounds, which make them dangerous to work with. The bomb that destroyed the Alfred P. Murrah Federal Building in Oklahoma City in 1995 was made of ammonium nitrate combined with fuel oil.[8] Nitrates also made headlines in 2013 when a fertilizer plant in West, TX exploded, killing 15 people and injuring more than 200 others. [9] Some companies are making efforts to create safer synthetic fertilizers with less explosive potential; Honeywell, for example, teamed up with J.R. Simplot to chemically fuse ammonium sulfate, which acts as a fire retardant, to ammonium nitrate, producing a stable molecule while retaining the ability to deliver nitrogen to crops.[8]

The more subtle, long-term problem with fertilizers is that they seep into streams and rivers and cause a host of environmental issues. The same nutrients that help crops grow on land also promote the growth of algae in waterways, creating so-called algae blooms. The algae can make waterways impassable, or worse, introduce toxins into drinking water. In 2014, researchers found elevated levels of a class of more than 90 compounds known as microcystins in the water supply of Toledo, OH. The compounds are produced by blue-green algae and are highly toxic to humans and other animals.[10]



Microcystin-LR

Microcystin-LR is the most common and most toxic of the microcystins. The two-letter nomenclature refers to the two amino acids, leucine and arginine, that distinguish it from other members of the class.

Reprinted in part from *C&EN*, **2014** 92 (32) 9

Scientists first detected dead zones in the Gulf of Mexico just west of the mouth of the Mississippi River in the 1970s; since then, that hypoxic area of water has sometimes grown to more than 8,000 square miles, or roughly the size of Connecticut. The area has now become more sensitive to the influx of agricultural chemicals, as the same amount of runoff causes even more growth now than it once did. Researchers led by University of Michigan ecologist Donald Scavia studied this shift in sensitivity and reported in 2007 that a 70% drop in nitrogen input would be required to shrink the dead zone to less than 2,000 square miles by 2015[12]—the target that was set forth by the EPA in its 2008 Gulf Hypoxia Action Plan.[13] In 2015, the EPA reported the Gulf of Mexico dead zone is 6,474 square miles—three times higher than the goal that was set back in 2008.[14]

The EPA and the inter-agency group known as the Hypoxia Task Force have since announced that shrinking the Gulf of Mexico dead zone will take two decades longer than expected. The new deadline for the goal of 2,000 square miles has been pushed back to 2035; in order to meet this goal, states will need to cut nutrient loads 20% by 2025.[15] Two recent studies from Iowa State University and Cornell University found that shifting to more diverse crop rotations could help Midwestern farmers reduce reliance on nitrogen fertilizers without causing food production to take a hit,[16] but it remains to be seen whether farmers will take steps in this direction.

IV. From Flush to Farm: The Controversy Over "Humanure"

Every year, farmers across the country apply roughly 4 million tons of "biosolids"—a polite term for specially processed sewage sludge—to their land.[17] This accounts for roughly 60% of the 6.5 million dry metric tons produced annually (according to the most recent national biosolids survey, conducted in 2004), and it covers about 1% of available farmland.

The idea is straightforward—sewage is rich with nutrients that plants need to grow. So why not return those nutrients to the land rather than bury them in landfills or incinerate them? It's a controversial issue, partly because the idea of applying human excrement to land used to grow food makes some people squeamish. But the larger issue is concern over the other chemicals present in biosolids that get added, along with the beneficial nutrients, to the soil, where they can potentially make their way into the food chain. Many unanswered questions remain about what effect these chemicals may have on the environment and human health.

A 2014 report funded by the U.S. Geological Survey and Colorado State University, Pueblo, found land fertilized with treated sewage sludge contains compounds found in many consumer products, including prescription drugs, flame retardants, fragrances, antibacterial agents, and potential endocrine disruptors.[18] The researchers analyzed a wheat field before and after biosolids were applied, and they found that about a dozen of the so-called "chemicals of emerging concern" had migrated as far as 50 inches into the soil, and that some of the compounds had made their way into the wheat plants.[19]

FOUND IN THE DIRT

Some of the synthetic compounds found in a wheat field spread with biosolids

CHEMICAL	USE
Bisphenol A	Thermal receipt paper, plastics
HHCB	Fragrance in consumer products
Nonylphenol ethoxylates[a]	Nonionic surfactants in detergents
Triclosan	Antibacterial soaps
Warfarin	Anticoagulant drug

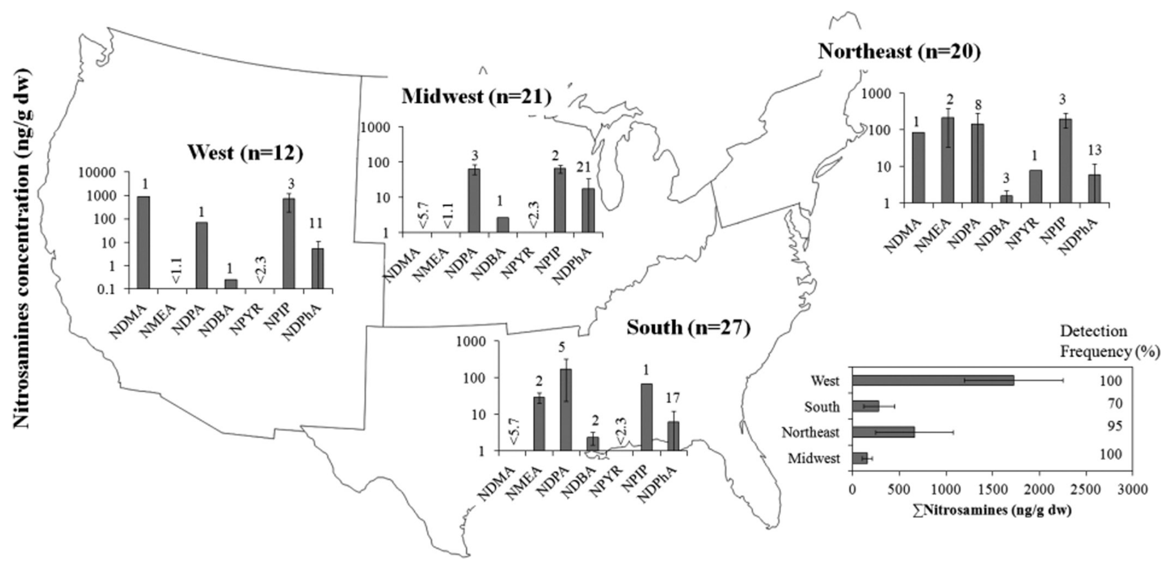
a Includes breakdown product nonylphenol.
HHCB = hexahydrohexamethylcyclopenta-2-benzopyran.
SOURCE: *J. Am. Water Resour. Assoc.* 2014, DOI: 10.1111/jawr.12163

Reprinted in part from *C&EN*, **2014** 92 (20) 6

The EPA currently has limits for levels of 10 contaminants in biosolids (nine heavy metals and fecal coliform), but does not regulate the hundreds of other chemicals that have been found in treated sewage sludge because, according to the EPA, the risks of those chemicals to human health and the environment are unknown at this time. Consequently, treatment plants are not required to remove them.

Numerous studies performed on biosolids in recent years have led some scientists and advocacy groups to express concern over what they call outdated federal regulations that may be putting the public at risk. These studies have revealed that processed sewage may also contain potentially carcinogenic nitrosamines,[20] perflourinated compounds,[21] nanomaterials,[22] pathogenic microbes,[23] and other pharmaceuticals and antimicrobial compounds.[24]

The myriad studies showing the presence of concerning chemicals in biosolids highlight the need for further study to understand where these compounds ultimately end up and if there is cause for concern.[20]



Spatial variation of *N*-nitrosamines concentrations in U.S. biosolids. The entry "*n*" is the total number of samples analyzed in the respective region. Numbers next to the bar depict the number of detects in the respective region. Error bars represent minima and maxima.

Reprinted in part from *Environ. Sci. Technol.*, 2014, 48 (9), pp 5085–5092 **DOI**: 10.1021/es5001352

V. Spotlight on Neonicotinoids: Concerns Over Effects on Pollinator Health

In recent years, several pesticides have come into the spotlight for concerns over their impact on the environment and wildlife. The use of a class of insecticides known as neonicotinoids has been on the rise since the early 2000s, replacing carbamates and organophosphates, the use of which was restricted after concerns over their effects on human health came to light.[3]

But several neonicotinoids have since come under fire as a result of research studies that suggest they adversely affect the behavior of bees. The pollinators—which are critical to agriculture—are believed to get exposed when dust from pesticide-coated seeds is released into the environment during planting, as well as through contact with the nectar and pollen of treated crops.[25]

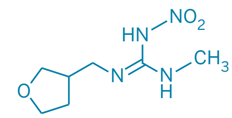
NEONICOTINOID TIMELINE OF RECENT EVENTS:

- **2012:** France proposes a ban on thiamethoxam, a Syngenta pesticide in the neonicotinoid family, after results published in the journal *Science* suggest that exposed bees had trouble returning to their hives after foraging.[26] The European Food Safety Authority (EFSA) calls for more research, stating that the levels tested were higher than what bees would encounter in the field.

- **2013:** EFSA reports that thiamethoxam, in addition to two other neonicotinoids known as clothianidin and imidacloprid, targets the nervous system of insects and cannot be ruled out as a cause of bee population decline in Europe. Agrochemical companies Syngenta and Bayer dispute the claims, however, saying the main cause of poor bee health and colony losses is the parasitic varroa mite. The EPA acknowledges a decline in honeybees in the U.S. but cites a lack of evidence linking neonicotinoids to the reductions.[27]

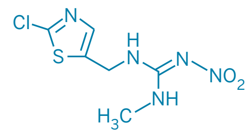
- **2013:** A study published in *Nature Communications* describes the mechanism by which neonicotinoids affect bee behavior. After treating bees with doses commonly found in pesticide-treated plants, the researchers found that imidacloprid and clothianidin deactivate brain cells that help bees learn. "If bees can't learn efficiently, then they can't forage efficiently," according to University of Dundee lead author Christopher N. Connolly. But critics say the findings of this study, which was performed on isolated bee brains, cannot be applied to bees in nature.[28]

- **April 2015:** The EPA announces restrictions on any new uses of four neonicotinoid pesticides—such as for applications to additional crops or applications via aerial spraying—until further notice while they evaluate the data suggesting a link between the chemicals and declines in bee populations. A pesticide industry trade association, CropLife America, criticizes the move, saying that it "will adversely impact growers' ability to meet future crop protection needs and access necessary products."[29]

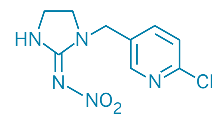


Dinotefuran

Thiamethoxam



Clothianidin



Imidacloprid

- **2015:** A few weeks after the EPA's announcement, two studies published in the journal *Nature* add to the mounting evidence against neonicotinoids. The reports showed that bees are attracted to the pesticides and that, under realistic conditions, the behavior and growth of bees in a crop field are affected. The latter study is described as "the first fully field-realistic, well-replicated trial so far," by University of Sussex biologist David Goulson. "It is no longer credible to argue that agricultural use of neonicotinoids does not harm wild bees," according to Goulson.[30]

In an effort to help curtail honeybee losses, seed industries have begun developing new products and processes to minimize the amount of pesticide to which bees are exposed.[31] Some companies are developing lubricants that help reduce the amount of pesticide-laden dust generated during planting, while others are exploring new polymers that help pesticides more firmly adhere to the seed.[31]

In early 2015, the Agriculture Committee of the U.S. House of Representatives announced plans to release a national pollinator health strategy. The EPA and USDA are leading this effort, which representatives say aims to balance both the need for crop protection and safeguarding pollinators from harmful pesticides.[32] According to a USDA survey, U.S. beekeepers lost 42% of their honeybees from April 2014 to April 2015, the second highest loss ever recorded. Neonicotinoids are one of many factors believed to be causing the mysterious disappearance of bees—a phenomenon known as colony collapse disorder—but scientists disagree over how much the various factors are to blame.

Also this year, the European Union announced plans to investigate restricting the use of 77 pesticides—a move that could affect roughly one-fifth of all pesticides licensed in Europe. Separately, France's agricultural minister introduced a policy to curb pesticide use in France, calling for a 25% reduction by 2020 and a 50% reduction by 2025.[33]

VI. Biotechnology and the Quest for Better Crops Through Science

Biotechnology, generally speaking, is the use of biological systems for making useful products. In agriculture, the primary example of modern biotechnology is the creation of crops that have been genetically engineered to have useful traits, such as resistance to pests and herbicides, enhanced nutrition, resistance to browning, or the ability to grow in extreme environments.

To create a genetically engineered crop, researchers must first identify a gene that encodes for the desired trait. It is not uncommon for agricultural biotechnology developers to evaluate more than 10,000 genes before they select one that is likely to succeed in commercial applications.[34] Researchers rely on the tools of bioinformatics, which allow them to use computers to predict whether the genes will have the desired function and to eliminate sequences that are similar to those of known allergens and toxins.[35]

From a pool of thousands of genetic sequences, researchers will often select approximately 500 for further evaluation. Scientists introduce the genes into plant cells using one of two methods. A technique known as microprojectile bombardment relies on brute force—strands of recombinant DNA are coated onto metal microparticles, then blasted into the cells with an instrument known as a biolistic gene gun. Once inside the cell, some of the DNA will insert itself into the plant's genome in a process known as homologous recombination. The second approach relies on a natural soil bacterium, known as *Agrobacterium tumefaciens*. Researchers place the cargo DNA into the plant-infecting bacteria, then the microbes transport the genetic payload into the plant's genome in a process known as transformation. Up-and-coming DNA editing technologies may one day offer researchers greater control over the exact positioning of the inserted genes *(see Sidebar: DNA-editing technologies may improve precision in biotech crops)*.

These new transgenic organisms are subjected to numerous tests. Scientists must verify that the gene is located in a position within the plant's genome that does not disrupt essential functions. They must also verify that the gene gets expressed at a suitable level and that the plant is able to pass the new gene on to its progeny. Finally, field tests reveal whether the transgenic crop is high-yielding and capable of expressing the desired trait in real-world conditions.[35] The majority of the crops evaluated at this stage will fail at one or more of these tests, but ideally, one strong candidate will be identified and then subjected to additional analyses and safety tests. These tests vary depending on a country's specific regulations, but they typically include side-by-side comparisons of the nutrient content of biotech crops with non-transgenic lines, evaluations of the crop's impact on the environment, and studies on the mode of action, toxicity, and allergenicity of the inserted trait.

DNA-EDITING TECHNOLOGIES MAY IMPROVE PRECISION IN BIOTECH CROPS

The two most popular approaches to creating biotech crops—microprojectile bombardment and infection with the bacterium *Agrobacterium tumefaciens*—suffer from the same downside: they insert DNA randomly into the host genome, which can result in the disruption or truncation of native genes with unknown consequences.

Scientists have been working to create more precise DNA-editing technologies, which may one day help agricultural chemists avoid the problem of random DNA insertion:

- Bacteria and archaea express DNA molecules known as clustered regularly interspaced short palindromic repeats, or CRISPRs, which can be designed to allow researchers to dictate exactly where a new gene will be inserted into a plant's genome.[37]
- Enzymes known as artificial restriction enzymes have two domains that enable them to bind to a specific DNA sequence and cleave the DNA at a precise location nearby. Two examples of artificial restriction enzymes are transcription activator-like effector nucleases[38] and zinc-finger nucleases.[39]

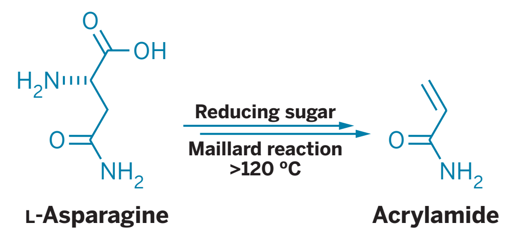
Farmers have been growing biotech crops since the mid-1990s. Today, 18 million farmers from 27 countries across the globe grow biotech crops, with the U.S., Brazil, Argentina, and India as the top producers. The most popular biotech crops are soybean, corn, and cotton. In the U.S., roughly 90% of all corn, cotton, canola, sugar beet, and soybeans are biotech varieties. On average, a biotech crop can take more than a decade and cost more than $100 million to develop.[36]

There are certainly ways to modify crops without the use of modern biotechnology. Farmers have used traditional breeding methods for centuries, crossing plants that have desirable traits with one another to yield new and improved varieties. Although organic farmers refrain from using biotech crops, organic standards across the globe do not prohibit the use of ionizing radiation to cause random mutations in a plant's genome, which can then be selected for desirable phenotypes. But biotech researchers say genetic engineering helps speed the process of creating better crops, which will be important as the world's population continues to grow toward an estimated 9 billion people by 2050.[1]

Commercialized biotech crops have primarily been focused on meeting farmers' needs. For example, soybeans resistant to the common pesticide glyphosate enable farmers to kill weeds without fear of harming the crop, and corn or cotton that express the pest-killing proteins known as Bt toxin (after their source, the bacterium *Bacillus thuringiensis*) allow farmers to reduce the amount of externally applied pesticide.

Yet there is enormous potential to develop biotech crops that have more direct benefits to consumers, such as enhanced nutrition.[41] For example, biotech firms DSM Nutritional Products and Monsanto are jointly developing a genetically engineered soybean oil that expresses high levels of the n-3 fatty acid stearidonic acid, which naturally converts in the human body into another heart-health-promoting n-3 fatty acid, eicosapentaenoic acid.[42] Without consumer demand for such products, however, companies take a risk investing the time and money to develop them.

Several recent examples highlight this struggle. The Idaho-based food and agribusiness company J. R. Simplot Company has created a genetically engineered potato that resists browning and expresses lower levels of asparagine, a naturally occurring amino acid that converts to the potentially carcinogenic compound acrylamide during frying.[43]



Reprinted in part from *C&EN*, **2014** 92 (46) 6

The company received safety clearance for the so-called Innate potatoes from the U.S. Food and Drug Administration (FDA) in early 2015. Also in early 2015, the USDA approved the first biotech apples, genetically engineered to resist browning by producing lower levels of polyphenol oxidase (PPO), an enzyme that causes apple flesh to turn brown. In the so-called Arctic apples, PPO levels are turned down through a process known as gene silencing, which uses RNA interference (RNAi) to inhibit its expression; no novel proteins are introduced and the nutrition and composition of the apples are otherwise equivalent to their conventional counterparts.[44]

The approval of both the modified apple and potato spurred numerous anti-biotech advocacy groups to put pressure on restaurants to refrain from using the biotech foods in their menus, warning of potential environmental, health, and economic risks.[45] Representatives of McDonald's restaurants, which sell 9 million pounds of French fries a day, released a statement shortly after the announcement for Innate potatoes, saying they do not plan to use them.

Public controversies, such as those mentioned above, typically center around concerns over food safety, environmental impact, and corporate control of the food and feed supply. For example, a recent cover story in *C&EN* highlighted the ongoing battle between organic farmers and their neighbors who are growing genetically engineered crops.[46] Producers of genetically modified seeds argue that regulations of GMO crops in the U.S. should be relaxed, because the scientific literature

TRANSGENIC CROPS WITH AN ENVIRONMENTAL BENEFIT

The term phytoremediation refers to the use of vegetation to clean up contaminated ground, for both agricultural and human use. Researchers have now found a way to engineer plants capable of metabolizing phenanthrene—a polycyclic aromatic hydrocarbon and possible carcinogen that is formed when coal, oil, or garbage are incompletely burned.[40]

The team, led by Shanghai Academy of Agricultural Sciences researcher Quean-Hong, inserted four bacterial genes into two plants—a model plant species *Arabidopsis* and a rice plant. The genes allow the plant to form a naphthalene dioxygenase complex that breaks down phenanthrene into less harmful metabolites. Most plant species used for phytoremediation get sickened through the process of sopping up contaminants from the soil; however, the genetically engineered varieties are able to absorb and metabolize the contaminants, and so the team found that they did not suffer toxic side effects. Plant scientist Om Parkas of the University of Massachusetts, Amherst, who was not involved in the study, tells *C&EN* that the transgenic plants are a "step in the right direction," but that more work is needed to make the plants more efficient at absorbing and metabolizing the pollutants.

THE GMO LABELING DEBATE

There is an ongoing debate over whether foods containing GMOs should bear a label stating so. Labeling advocates argue that consumers have a right to know what is in their food, while opponents state that mandatory labeling would provide no useful information, because whether a food contains GMOs does not affect its safety. In Congress, legislation that would prohibit requirements for GMO labeling cleared the House of Representatives in July 2015 by a vote of 275-150. The so-called "Safe & Accurate Food Labeling Act of 2015" includes a voluntary federal program to certify GMO-free foods.[47] According to a recent survey conducted by the Pew Research Center, more than half of the general public views GMO foods as unsafe, although data from a survey conducted by the International Food Information Council found that in practice, only about 2% of the U.S. population shun GMOs in food.[48]

Despite the lack of evidence that GMO foods are more harmful to human health than their conventional counterparts, public doubt about the safety of GMOs appears to be rising.[48] Some experts suspect this is because the FDA does not require companies to submit traditional toxicity data prior to introducing new GMOs to the market. Instead, companies must demonstrate that a new GMO food is not substantially different compared to its non-GMO counterpart in nutrient and allergen content. Although companies typically provide the FDA with additional data—including molecular characterization of the inserted DNA and the resulting products expressed from that DNA, acute toxicity test data on any new proteins formed, allergenicity assessments, and complex compositional analyses—GMO labeling proponents point out that all of these safety assessments are conducted by the food industries themselves, which have vested interests in seeing their products succeed.

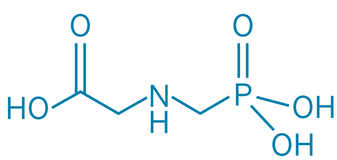
supports the notion that GMOs are safe for the environment and human consumption. But organic farmers say the USDA should boost testing and oversight of GMO products once they hit the market, arguing that the current regulatory process does not address the possibility of contamination of organic farmland—known as genetic drift—with genetically engineered seeds. Organic farmers then suffer losses as a result of having grown their crops using organic practices but being unable to sell them on the organic market due to contamination with GMOs.

In addition to issues regarding contamination, there is an ongoing debate over whether foods containing GMOs should be required to be labeled as such *(see Sidebar: The GMO labeling debate)*. The White House plans to organize several public meetings soon, which will "help sort through all of the thorny issues swirling around GMO crops and to guide federal agencies toward developing a new system for overseeing biotechnology."[46]

VII. When Nature Fights Back: Battling Weed Resistance

One of the most popular genetically engineered traits encodes resistance to the common herbicide glyphosate, which is marketed by agricultural giant Monsanto as Roundup. Glyphosate has been the best-selling herbicide since 2001, and the majority of cultivated acres in the U.S. are home to herbicide-tolerant corn, soybeans, and cotton. These so-called "Roundup ready" crops, which were introduced to the market in 1996, enable farmers to spray glyphosate to kill weeds without harming their crop. But over time, herbicide resistance develops, sending farmers and agronomists into a kind of arms race against weeds that are getting tougher to kill.[49]

Glyphosate kills weeds by inhibiting an enzyme, known as 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which is essential for plant growth. Since the introduction of Roundup ready crops, glyphosate use has steadily risen—and along with it, glyphosate resistant varieties of weeds. According to the International Survey of Herbicide Resistant Weeds, there are now 15 strains of weeds that have acquired resistance to glyphosate.[50]



Glyphosate

In 2015, second-generation herbicide-tolerant crops, produced by both Monsanto and Dow AgroSciences, received approval by the USDA.[51] These crops can survive treatment with both glyphosate as well as either 2,4-dichlorophenoxyacetic acid (2,4-D) or 3,6-dichloro-2-methoxybenzoic acid (dicamba). Both 2,4-D and dicamba have been in use for more than 40 years. With these crops, farmers can continue to use glyphosate as the first line of defense against weeds, and if resistance is discovered, they can add 2,4-D or dicamba without worrying about crop damage.

Yet several consumer, environmental, and farmer groups oppose the approval, arguing that overreliance on chemical controls, rather than nonchemical weed control methods such as crop rotation, will simply lead to the further development of weed resistance. Indeed, "evolutionary nature is such that when you put enough selection pressure on a species, it will develop resistance," Mississippi State University researcher David R. Shaw told *C&EN*.[49] There is also the concern that spikes in herbicide use will be accompanied by increased health risks and pollution. But researchers at Dow AgroSciences note that the 2,4-D used in their herbicide mixture is a new salt form, known as 2,4-D choline, that is less prone to volatilization and environmental drift.[51] Data collected by the company show a roughly 90% reduction in both volatility and drift. Monsanto's new formulation of dicamba is also reported to have reduced volatility compared with previous formulations.[49]

Another approach to battling weed resistance involves the discovery and development of pesticides derived from nature that are more specific and more likely to delay the onset of the development of resistance.[2] Synthetic pesticides typically bind to one or a few sites to ultimately lead to a pest's demise, and researchers in some agricultural start-ups are beginning to look for molecules that target several sites. Researchers at one such company, AgriMetis, are currently working toward this end, performing high-throughput screening of natural products to discover potential multi-target pesticides.[2]

VIII. The Complex Relationship Between Climate Change and Agriculture

The relationship between climate change and agriculture is a two-way street: Agriculture contributes to climate change and then in turn is affected by the changing climate. A whopping one-third of the carbon dioxide that humans have added to the atmosphere has been released as a result of cutting, burning, and plowing forests and grasslands to convert them to cropland, according to University of Washington geologist David R. Montgomery.[53] And continued plowing over the years continues to stir up organic-rich top soil, causing soil erosion and releasing more CO_2 into the atmosphere. As global temperatures and atmospheric CO_2 levels rise, some crops grow better, while others fare worse, and the overall impact depends on a host of other factors.

The goals of sustainable agriculture are to "produce enough food for everyone, protect natural resources, and prove financially viable for growers and consumers," Bayer CropScience CEO William Buckner said in 2010 at a National Policy Conference.[41] In an effort to protect natural resources and reverse the trend of carbon release from soil, policymakers, scientists, and environmental groups are encouraging farmers to adopt land-management practices that replenish carbon in the soil and help offset agricultural carbon emissions.

One strategy for sequestering carbon in the soil is the age-old technique of applying compost and manure, including biosolids. Other techniques include planting cover crops, such as alfalfa and rye, and conservation tillage, which leaves about a third of a crop to reside on the soil surface in an effort to help reduce the amount of soil erosion. These practices can potentially benefit both the farmer and the environment, as they often lead to higher yields and improved water retention.[53] However, the climate mitigation impact is hard to predict, largely because many factors, such as climate, type of crop, farming practice, and site history must be taken into account.

To help with these predictions, researchers at the Climate Friendly Farming initiative at Washington State University (WSU) have developed CropSyst, a predictive model that integrates the results of agricultural studies. The team found the most effective practice for increasing carbon storage is replacing synthetic inorganic fertilizers with organic sources of fertilizer, including both animal manure and biosolids. However, biosolids are limited—if all sewage sludge in the U.S. were used on farmland, it would cover only 1% of arable land—and their use is controversial because of the presence of pharmaceuticals, pathogens, and industrial chemicals The use of animal manure comes with its own risks, since it can contain concerning levels of antibiotics that contribute to the growing problem of antibiotic resistance. WSU researchers are working on the development of anaerobic digestion technologies that would help decontaminate animal waste to create safer organic fertilizer, while simultaneously producing biogas, a useful, methane-rich, renewable byproduct that can be captured and used in place of fossil fuels for heating and transportation.[53]

The rise in global temperatures and atmospheric CO_2 can be beneficial for some crops in some places, assuming that other conditions are met, such as nutrient levels, soil moisture, and water availability.[54] But greater frequency and severity of droughts and floods pose obvious challenges for farmers. Although warmer temperatures help many crops grow more quickly, they tend to suffer from lower yields, since faster growth means seeds don't have as much time to grow and mature. To predict the overall effect of climate change on a crop, one must take into consideration the crop's optimal temperature and the degree to which elevated CO_2 boosts yields. Doubling CO_2 concentrations results in a 30% yield increase for wheat and soybeans, yet provides a less than 10% increase for corn. But if the temperature rises above the crop's ideal, the yield increases may be reduced. Additionally, many weeds, pests, and fungi thrive under conditions of elevated temperatures and CO_2 levels, and the increased use of pesticides is accompanied by environmental and health risks.[54]

Researchers at the National Science Foundation (NSF) and the U.S. Departments of Energy and Agriculture have teamed up to help develop computer models for predicting the impacts of climate change on society, including its impacts on the production of food and renewable fuels.[55] The impacts of climate change, including droughts, ecosystem stress, and reduced agricultural productivity, "are becoming more profound and immediate than anticipated," noted NSF director Arden Bement at a 2010 briefing launching the initiative, according to *C&EN*. "We know we need to act and to act quickly."

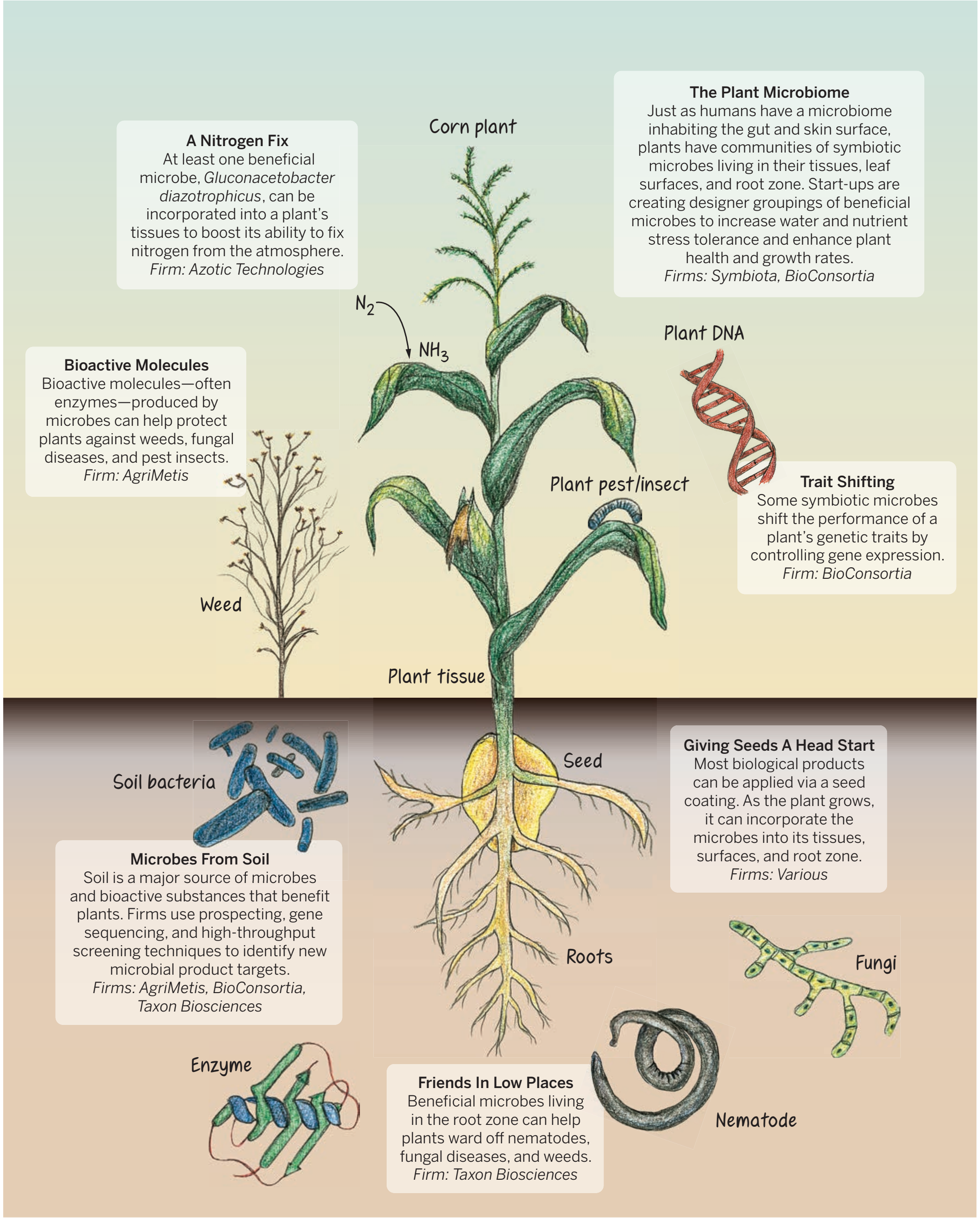
IX. Boosting Crop Production With Biological Agents

An increasing number of agriculture industries are looking to biological organisms and plant-derived compounds for boosting crop productivity. The move is sparked by the high cost and increasing number of regulatory hurdles associated with developing new chemical pesticides, as well as the rise in pest resistance to the most widely used synthetic compounds. While traditional agrochemicals can take 10 years and cost upwards of $260 million to develop, a beneficial microbe can accomplish the same task in two years for $3 million, according to research analyst Michael Cox.[56,57]

Beneficial microbes are to plants what probiotics are to people. Researchers have discovered that some strains of bacteria and fungi form symbiotic relationships with roots and seeds to help make plants more efficient and productive, while others support plant growth by helping to thwart disease.[56] For example, the nitrogen-fixing rhizobacteria are known to help leguminous plants take up more nitrogen, and two strains of bacteria—*Bacillus subtilis* and *Bacillus licheniformis*—work together to help sugarcane plants resist attack from nematodes. It turns out microbes and fungi, since they face environmental pressures similar to those faced by plants, have developed chemical defenses against many pests, and these same defenses can be exploited for the benefit of commercial crops.[2]

One of the biggest challenges to using beneficial microbes is getting them to work predictably, because their performance can vary depending on soil composition and moisture, as well as temperature and the type of plant to which they are applied.[56] Microbiologists have found that in many cases, microbes perform better together than alone, since their metabolisms may complement each other or they may have different optimal temperatures, which can help the group survive even as conditions change.[2] The numerous ways microbes and other biological agents can benefit plants are illustrated in the figure to the right.

In recent years, scientists in the crop protection business have begun looking more to nature for inspiration and answers. This notion is nothing new—the ancient poem widely known as the Lithica, circa 400 B.C., reads, "All the pests that out of Earth arise, the Earth itself the antidote supplies."[57] At the Fall 2012 ACS National Meeting in Philadelphia, scientists discussed the shift away from synthetic chemicals and toward natural products for pest management,.[57] For many millennia, plants have been evolving biomolecular mechanisms for protection against myriad pests. "Nature seems to make with great facility those compounds that the chemist makes with great difficulty, if at all," said University of Mississippi natural products chemist Stephen J. Cutler.



Reprinted in part from *C&EN*, **2015** 93 (19) 10

Enter chemists in the 20th century, who used the tools of organic synthesis to create synthetic compounds for crop protection. Many of these worked well for a time, but not without a cost, as over time many of these chemicals turned out to have adverse effects on human health and the environment and ultimately accelerated the development of pest resistance, which remains one of agriculture's greatest challenges to date.

Natural products may very well hold the key to better, safer pesticides, and the numbers seem to suggest that agricultural industries believe so. Between 1997 and 2010, nearly

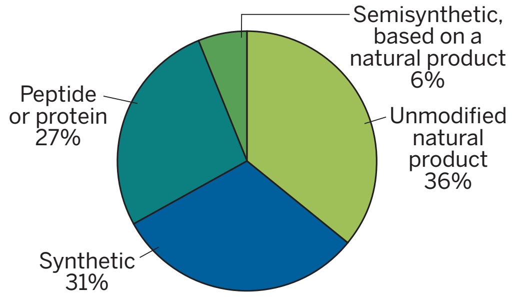
RNA INTERFERENCE FOR BATTLING THE TOUGHEST PESTS

The earliest examples of RNA interference (RNAi) for killing pests date back nearly a decade, when researchers inserted DNA into the nuclei of a plant. The DNA encoded for a strand of interfering RNA that, upon consumption by a pest, binds to a complementary strand of RNA in the pest's cells, ultimately leading to its demise. Yet the early demonstrations of RNAi approaches to battling pests fell short, as they were unable to kill all pests, presumably as a result of the RNAi getting partially metabolized in the cytoplasm of plant cells.

In March 2015, researchers led by Ralph Bock at the Max Planck Institute for Molecular Plant Physiology reported a way around this problem. The team developed a new strand of RNAi capable of killing the Colorado potato beetle,[58] an international super pest that costs the agricultural industry billions of dollars each year and has become increasingly tougher to eradicate in recent years, due to growing resistance against all major classes of insecticides. The team made a modification to earlier RNAi strategies—they inserted instructions to guide the double-stranded RNAi molecule into the plant cells' chloroplasts, rather than their nuclei. The change resulted in full crop protection from the Colorado potato beetle.

Another approach to battling pests involves RNAi that is sprayed onto plants, rather than genetically engineered into their genomes. Several companies, including Monsanto, Bayer, and Syngenta, are currently developing these so-called genetic sprays.[59]

70% of the 277 pesticides registered had their basis in a natural product, according to USDA scientist Charles L. Cantrell. The trend may also be attributed to increasing regulatory pressure to eliminate toxic, older synthetic pesticides, as well as farmers' interests in better tools for pest management and the growing consumer demand for foods with lower pesticide residues.[57] Cantrell is careful to point out that just because a pesticide is derived from nature does not automatically make it safer than its synthetic counterparts. "Some natural products in their natural form can be quite toxic," he told *C&EN*. "But they tend to degrade quicker in the environment than traditional synthetic organophosphate and halogenated pesticides, are more selective against the target, and can be used at lower application rates."



EPA-registered pesticide active ingredients, 1997–2010 = 277

Reprinted in part from *C&EN*, **2012** 90 (36) 66

X. The Inextricable Link Between Technology and Agriculture

The World Hunger Education Service (WHES) reports that there is already enough food generated in the world to feed everyone on the planet.[60] In fact, the per capita food availability has jumped from 2220 kcal/person/day in the 1960s to 2790 kcal/person/day in the early 2000s, and the proportion of chronically undernourished in the world population has dropped from roughly one-third to one-sixth in the same time span. However, this means that 805 million of the world's 7.3 billion people are still chronically undernourished, and the vast majority—791 million—live in developing countries. "The principal problem is that many people in the world still do not have sufficient income to purchase (or land to grow) enough food," the WHES reports.[60] And yet undernourishment is not just a problem in developing countries. A 2008 report from the USDA states that nearly 15% of U.S. households had low or very low food security, which has led the Obama Administration to make food security a priority.[61]

A host of new agricultural start-up companies have sprung up in recent years, many of them focused on environmentally sustainable approaches to increasing yields while reducing the need for fertilizers, pesticides, water, and energy.[2] These companies—which include Symbiota, Taxon Biosciences, AgriMetis, NexSteppe, and Blue River Technology—bear the so-called "cleantech" label, which helps them attract funding and be competitive against agricultural industry giants like BASF, Bayer, Dow Chemical, DuPont, Monsanto, and Syngenta.

While larger agricultural firms have typically focused on developing and selling tried-and-true seeds, resistance traits, and chemicals like pesticides for crop protection, the new start-ups have found open space for innovation in technologies for field automation, as well as bio-based strategies for crop enhancement, such as beneficial microbes and natural pest control products. Technology is becoming increasingly intertwined with modern agriculture. GPS monitoring, field automation,

FEEDING THE WORLD: MORE THAN JUST BOOSTING CROP YIELDS

Boosting crop yields may not be the entire solution, but it is at least part of it. The United Nations Food & Agriculture Organization predicts food production will need to increase 70% by 2050,[61] when the world population is expected to surpass 9 billion.[1]

There is much disagreement over the best way forward. Some researchers, like Harvard University political scientist Robert Paalberg, say farmers in developing countries need access to science-intensive "precision farming" techniques and genetically engineered crop varieties that will help them grow high-yielding crops even in unfavorable conditions. But others, such as Slow Food USA president Joshua Viertel, are concerned that biotech companies see the food gap as a marketing opportunity and are more interested in boosting profits than solving world hunger. It is essential to provide farmers access to good, affordable technologies, Viertel told *C&EN,* but the strategy should emphasize low-cost, locally available inputs over expensive biotech seeds.[61]

and data analysis are just some of the tools that help farmers make decisions about when to plant and water, and how much fertilizer and pesticide to apply to maximize their resources.[2] Other up-and-coming technologies are part of a field often called "precision agriculture;" these include the use of robots, environmental satellites, drones, real-time imaging, and smart phones, which can help farmers make decisions about planting and treating their fields at resolutions as low as 1 cm. One technology, developed by Blue River Technologies, uses real-time imaging to distinguish between desired and undesired plants and weeds, and allows fertilizer to be applied directly to the leaves of the desired plants. The company is now developing technologies for automatic weeding, CEO Jorge Heraud told *C&EN*.[2] The potential benefits of these technologies, which Heraud describes as "plant-by-plant farming," include both reduced costs to farmers and reduced environmental harm.

XI. Overview and Future Outlook

Agricultural chemistry is an exciting and highly multidisciplinary research area that combines the skills of chemists, biochemists, microbiologists, environmental scientists, and engineers. Over the years, chemists have played a vital role in the development of pesticides, fertilizers, and genetically modified seeds, as well as beneficial microbes and natural products. Agricultural chemistry is arguably one of the only research fields whose impact is felt the world over, as everyone on the planet needs to eat to survive.

The challenges in agriculture today are numerous and great. What must be done to feed more people with less land? And how can this be accomplished without unnecessarily burdening the environment? What must farmers do to both adapt to and minimize farming's contributions to climate change? How will agricultural methods change with the advent of new technologies? And how will strategies for increasing access to food differ between developed and developing nations?

As the global population continues to rise, advancements in agriculture will be ever more critical, and the skills of chemists will continue to be essential for tackling the field's toughest challenges.

XII. References

[1] United Nations Department of Economic and Social Affairs. "World population projected to reach 9.6 billion by 2050" (report), June 13, 2013; available online at http://www.un.org/en/development/desa/news/population/un-report-world-population-projected-to-reach-9-6-billion-by-2050.html.

[2] Bomgardner, M. M. " Entrepreneurs See A New Field Of Dreams In Agriculture." *Chem. Eng. News* 2015 *93*(19): 8-12.

[3] Fernandez-Cornejo, J., Nehring, R., Osteen, C., Wechsler, S., Martin, A., and Vialou, A. "Pesticide Use in U.S. Agriculture: 21 Selected Crops, 1960-2008" (Economic Information Bulletin EIB-124); U.S. Department of Agriculture, May 2014; available online at http://www.ers.usda.gov/publications/eib-economic-information-bulletin/eib124.aspx.

[4] American Chemical Society. "Legacy of Rachel Carson's Silent Spring." National Historic Chemical Landmark information booklet, October 2012; available online at http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/rachel-carson-silent-spring.html.

[5] Darby, W. J. "Silence, Miss Carson." *Chem. Eng. News* **1962** 40(40): 60-63.

[6] Erickson, B. E., "Common Herbicide Used In Monsanto's Roundup Deemed 'Probably Carcinogenic'." *Chem. Eng. News* **2015** 93(13): 5.

[7] Dittmar, H., Drach, M., Vosskamp, R., Trenkel, M. E., Gutser, R., and Steffens, G. "Fertilizers, 2. Types." *Ullmann's Encyclopedia of Industrial Chemistry*, published online July 2009; available at http://onlinelibrary.wiley.com/doi/10.1002/14356007.n10_n01/abstract;jsessionid=7865783335977AE45BC8411BADF3D213.f01t02.

[8] Bomgardner, M. M. "Safer Fertilizer." *Chem. Eng. News* (web date Dec. 6, 2011); available online at http://cen.acs.org/articles/89/web/2011/12/Safer-Fertilizer.html.

[9] Johnson, J. "Deadly Fertilizer Explosion." *Chem. Eng. News* **2013** *91*(16): 8.

[10] Wilson, E. "Danger From Microcystins In Toledo Water Unclear." *Chem. Eng. News* **2014** *92*(32): 9.

[11] Brown, V. "Downsizing the Gulf of Mexico's Dead Zone." *Chem. Eng. News* (web date July 16, 2010); available online at https://pubs.acs.org/cen/news/88/i29/8829news4.html.

[12] Scavia, D., and Donnelly, K. A. "Reassessing Hypoxia Forecasts for the Gulf of Mexico." *Env. Sci. Technol.* **2007** *41*(23): 8111-8117.

[13] U.S. Environmental Protection Agency. "Gulf Hypoxia Action Plan 2008 for Reducing, Mitigating, and Controlling Hypoxia in the Northern Gulf of Mexico and Improving Water Quality in the Mississippi River Basin" (report of the Mississippi River/Gulf of Mexico Watershed Nutrient Task Force). Washington, DC, 2008; available online at http://water.epa.gov/type/watersheds/named/msbasin/actionplan.cfm.

[14] U.S. Environmental Protection Agency. "Northern Gulf of Mexico Hypoxic Zone" (report of the Mississippi River/Gulf of Mexico Watershed Nutrient Task Force). Washington, DC, 2015; available online at http://water.epa.gov/type/watersheds/named/msbasin/zone.cfm.

[15] Morrison, J. "Shrinking of Gulf 'Dead Zone' Postponed." *Chem. Eng. News* **2015** *93*(8): 31.

[16] (a) Davis, A. S., Hill, J. D., Chase, C. A., Johanns, A. M., and Liebman, M. "Increasing Cropping System Diversity Balances Productivity, Profitability and Environmental Health. *PLoS ONE* **2012** *7*(10): e47149. (b) Blesh, J., and Drinkwater, L. E. "The impact of nitrogen source and crop rotation on nitrogen mass balances in the Mississippi River Basin. *Ecol. Appl.* **2013** *23*(5): 1017-1035.

[17] Lu, Q., He, Z. L., and Stoffella, P. J. "Land Application of Biosolids in the USA: A Review." *Appl. Env. Soil Sci.* **2012** *2012*, article ID 201462; available online at http://www.hindawi.com/journals/aess/2012/201462/.

[18] Yager, T. J. B., Furlong, E. T., Kolpin, D. W., Kinney, C. A., Zaugg, S. D., and Burkhardt, M. R. "Dissipation of Contaminants of Emerging Concern in Biosolids Applied to Nonirrigated Farmland in Eastern Colorado." *J. Am. Water Resources Assoc.* **2014** *50*(2): 343-357.

[19] Hogue, C. "Down The Drain Doesn't Mean They're Gone." *Chem. Eng. News* **2014** 92(20): 6.

[20] Kollipara, P. "Treated Sewage Solids Contain Troubling Nitrosamines." *Chem. Eng. News* (web date April 23, 2014); available online at http://cen.acs.org/articles/92/web/2014/04/Treated-Sewage-Solids-Contain-Troubling.html.

[21] Renner, R. "Sludge Sloughs Off Perfluorinated Chemicals." *Chem. Eng. News* (web date April 8, 2011); available online at http://cen.acs.org/articles/89/web/2011/04/Sludge-Sloughs-Off-Perfluorinated-Chemicals.html?type=paidArticleContent.

[22] Wolf, L. K. "Moving Up The Food Chain." *Chem. Eng. News* **2011** *89*(11): 44-46.

[23] Gertz, E. "Safety Rules For Sewage Sludge May Be Outdated." *Chem. Eng. News* (web date June 15, 2011); available online at http://cen.acs.org/articles/89/web/2011/06/Safety-Rules-Sewage-Sludge-Outdated.html.

[24] Zurer, R. A. "Crops Absorb Pharmaceuticals From Treated Sewage." *Chem. Eng. News* (web date Aug. 2, 2010); available online at http://cen.acs.org/articles/88/web/2010/08/Crops-Absorb-Pharmaceuticals-Treated-Sewage.html.

[25] Erickson, B. E. "Bee Study Prompts Action." *Chem. Eng. News* **2013** *91*(6): 9.

[26] Bomgardner, M. M. "Bee-Linked Pesticide Under Fire." *Chem. Eng. News* **2012** *90*(24): 9.

[27] Scott, A. "Stinging Attack on Bee Study." *Chem. Eng. News* **2013** *91*(4): 8.

[28] Drahl, C., and Erickson, B. E. " Pesticides Shown To Damage Bee Brains." *Chem. Eng. News* **2013** *91*(13): 13.

[29] Hess, G. " EPA Halts New Uses Of Pesticides Linked To Bee Decline." *Chem. Eng. News* **2015** *93*(15): 8.

[30] Erickson, B. E. "Evidence Against Neonicotinoids Mounts." *Chem. Eng. News* **2015** *93*(17): 5.

[31] Erickson, B. E. "Curtailing Honeybee Losses." *Chem. Eng. News* **2013** *91*(12): 30-32.

[32] Erickson, B. E. "Congress Puts Pressure On Obama Administration To Release Pollinator Protection Plan." *Chem. Eng. News* **2015** *93*(20): 8.

[33] Scott, A. "Europe Seeks to Curb Pesticides." *Chem. Eng. News* **2015** *93*(6): 4.

[34] Phillips McDougall Ltd. "The Cost of New Agrochemical Product Discovery, Development and Registration in 1995, 2000 and 2005-8" (consultancy study for Crop Life America and the European Crop Protection Association), January 2010; available online at http://croplife.org/wp-content/uploads/2014/04/Phillips-McDougal-Research-and-Development-study.pdf.

[35] Privalle, L. S., Gillikin, N., and Wandelt, C. "Bringing a Transgenic Crop to Market: Where Compositional Analysis Fits." *J. Agric. Food Chem.* **2013** *61*(35): 8260-8266.

[36] Herman, C. "Biotechnology: Using Living Systems to Solve Problems." *Inform* magazine (AOCS), February 1, 2015, pp. 70-75.

[37] Marraffini, L. A., and Sontheimer, E. J. "CRISPR interference: RNA-directed adaptive immunity in bacteria and archaea." *Nat. Rev. Genetics* **2010** *11*(3): 181-190.

[38] Boch, J. "TALEs of genome targeting." *Nat. Biotechnol.* **2011** *29*(2): 135-136.

[39] Carroll, D. "Genome Engineering With Zinc-Finger Nucleases." *Genetics* **2011** 188(4): 773-782.

[40] Madhusoodanan, J. "Transgenic Plants Sop Up Soil Pollutants." *Chem. Eng. News* (web date Oct. 29, 2014); available online at http://cen.acs.org/articles/92/web/2014/10/Transgenic-Plants-Sop-Soil-Pollutants.html.

[41] Erickson, B. E. "Modern Agriculture." *Chem. Eng. News* **2010** 88(33): 39.

[42] Harris, W. S., Lemke, S. L., Hansen, S. N., Goldstein, D. A., Su, H., Nemeth, M. A., Taylor, M. L., Ahmed, G., and George, C. "Stearidonic Acid-Enriched Soybean Oil Increased the Omega-3 Index, an Emerging Cardiovascular Risk Marker." Lipids **2008** *43*(9): 805-811.

[43] Drahl, C., and Morrison, J. "Modified Spud Gains Approval." *Chem. Eng. News* **2014** 92(46): 6.

[44] Erickson, B. E. "Department Of Agriculture Approves First Genetically Modified Apple, Which Resists Turning Brown." *Chem. Eng. News* **2015** *93*(8): 5.

[45] Erickson, B. E. "FDA Approves Genetically Modified Apple And Potato." *Chem. Eng. News* **2015** *93*(13): 8.

[46] Erickson, B. E. "Rethinking Biotech Rules." *Chem. Eng. News* **2015** *93*(29): 25-26.

[47] Erickson, B. E. "House Passes GMO Food Labeling Legislation." *Chem. Eng. News* **2015** *93*(30): 41.

[48] Erickson, B. E. "Rising Public Doubt About the Safety of Genetically Modified Food." *Chem. Eng. News* **2015** *93*(14): 20-21.

[49] Bomgardner, M. M. "War on Weeds." *Chem. Eng. News* **2012** *90*(21): 20-22.

[50] Erickson, B. E. "Rocky Road for Roundup." *Chem. Eng. News* **2015** *93*(37): 10-15.

[51] Tullo, A. H. "Dow Battles Back." *Chem. Eng News* **2014** *92*(47): 19.

[52] Erickson, B. E. "USDA Clears Use of Two Modified Crops." *Chem. Eng. News* **2015** *93*(22): 23.

[53] Lockwood, D. "Returning Carbon To The Farm." *Chem. Eng. News* **2013** *91*(28): 26-27.

[54] U.S. Environmental Protection Agency. "Climate Impacts on Agriculture and Food Supply" (online overview); available online at http://www.epa.gov/climatechange/impacts-adaptation/agriculture.html.

[55] Erickson, B. E. "Predicting Climate Change Impacts." *Chem. Eng. News* **2010** *88*(13): 17.

[56] (a) Reisch, M. S. "Growing Profits with Microbes." *Chem. Eng. News* **2014** *92*(37): 23-25; (b)

[57] Ritter, S. K. "Pesticides Trend All-Natural." *Chem. Eng. News* **2012** *90*(36): 64-67.

[58] Everts, S. "New Insecticidal Strategy Kills Crop Pests With RNA Interference." *Chem. Eng. News* **2015** *93*(9): 7.

[59] Regalado, A. "The Next Great GMO Debate." *MIT Technol. Rev.* (web date Aug. 11, 2015); available online at http://www.technologyreview.com/featuredstory/540136/the-next-great-gmo-debate/.

[60] World Hunger Education Service. "2015 World Hunger and Poverty Facts and Statistics" (online report); available online at http://www.worldhunger.org/articles/Learn/world%20hunger%20facts%202002.htm.

[61] Erickson, B. E. "Feeding the World." *Chem. Eng. News* **2010** *88*(13): 18-19.

ACS
Chemistry for Life®

AMERICAN CHEMICAL SOCIETY
1155 SIXTEENTH STREET, NW
WASHINGTON, DC 20036
www.acs.org