PEST RESISTANCE and FAILED EFFICACY

RESISTANCE | AUGUST 2, 2023

The Growing Insecticide Resistance Issue Increases Concerns Over Deadly Disease Transmission Through Mosquitoes

A study published in *Pest Management Science* finds resistance to insecticides like pyrethroids are challenging attempts to control the mosquito *Aedes aegypti* (*Ae. aegypti*), the primary transmitter (vector) of dengue fever. While this study takes place in Bangladesh, resistance to biocides—whether to antibiotics, antimicrobials, or pesticides—is growing globally. Prevention of disease outbreaks is threatened by reliance on chemical biocides to which pathogens and their vectors develop resistance. In fact, resistance is predicted by elementary population genetics, and the speed of its evolution is directly related to the toxicity—that is, the strength of selection pressure—and inversely related to the generation length of the organism. (See PAY articles here and here, a PBS article here.)

Insecticide resistance has been an issue since the introduction of DDT (dichlorodiphenyltrichloroethane) in the 1940s. Although most countries currently ban DDT use, the compound is not the only chemical pesticide promoting pest resistance. Several current-use insecticides pose the same threat. Areawide, indiscriminate spraying of insecticides is causing resistance to develop among many pests. Mosquitoes have become increasingly resistant to synthetic pyrethroids, in addition to other classes of insecticides, such as carbamates and organophosphates. Thus, this study demonstrates the need for sustainable and practical strategies to combat the growing disease burdens.

The study notes, "Intensive use of pyrethroids in Dhaka has selected for highly resistant mosquito populations, which was confirmed through bioassays. This pyrethroid resistance is associated with high frequencies of the *V1016G kdr* mutation and activities of detoxifying enzymes. As evidenced from our free-flight experiments, the effective operational use of pyrethroids in control programs is compromised and, therefore, requires reconsideration. […] Ultimately, scalable and sustainable non-insecticide-based approaches such as Wolbachia-based population replacement could have an important role in curbing Aedes-borne diseases in Bangladesh."

Researchers from the QIMR Berghofer Medical Research Institute, Australia, examined the common insecticides used in Dhaka, Bangladesh, to determine the mechanisms and intensity of insecticide application driving resistance. The pyrethroid insecticides tested include permethrin and deltamethrin. Using a bottle assay, the research measures the mortality percentage of mosquitoes after insecticide exposure. The study finds *Ae. Aegypti* mosquito colonies display significantly higher levels (high-intensity) of resistance to pyrethroids. Although the mortality rate of mosquitoes exposed to permethrin is much lower than deltamethrin (2–24 percent mortality and 48–94 percent mortality, respectively), the metabolic mechanisms involved are the same. Specifically, responses to the synergistic reaction between pyrethroids induce multifunction oxidases, esterases, and glutathione S-transferases. Moreover, a high frequency of knockdown resistance (kdr) alleles for resistance indicates a V1016G mutation, conferring resistance to deltamethrin. Although exposure can replace host-seeking behavior, this effect is only temporary. Since over 74 percent of mosquitoes from colonies in Dhaka survive initial exposure to pyrethroids, increased disease prevalence is likely.

Associate Professor Gregor Devine, PhD, at the Mosquito Control Laboratory, said, "'The use of pyrethroids in Dhaka is no longer effective, and the control program needs to switch to a different approach. The study suggests the presence of high levels of insecticide resistance among *Ae. aegypti* populations may have contributed to the escalating dengue burden."

This study is part of an all too familiar phenomenon of resistance among pest populations. Scientists note that resistance is an entirely normal, adaptive phenomenon: organisms evolve, "exploiting" beneficial genetic mutations that give them a survival advantage. However, resistance is growing in all sectors of pest control, including agriculture and medicine. For nearly a century, the chemical industry response to resistance is the development of a compound that kills the resistant organism (whether insect or weed or bacterium or fungus), which works for a while. However, the dependence on chemical solutions is increasingly failing. Whether it is antibiotics for bacterial infections, herbicides for weeds/pests, or insecticides to mitigate vector-borne diseases, organisms are becoming resistant to usually toxic compounds. Once an organism inevitably becomes resistant to a particular chemical control strategy, people—the chemical industry, researchers, applicators, farmers, public health workers, clinicians, et al.—will have typically moved on to the subsequent chemical "solution." Pesticide Action Network North America (PANNA) notes, "The World Health Organization underscored the problem in their 2012 guidance on policymaking for Integrated Vector Management (IVM): 'Resistance to insecticides is an increasing problem in vector control because of the reliance on chemical control and expanding operations.... Furthermore, the chemical insecticides used can have adverse effects on health and the environment.'"

Beyond Pesticides has written extensively on the issue of resistance, particularly the relationship to the use of agricultural and other land management pesticides, with the central message: resistance is a symptom of the ineffectiveness of chemical-intensive agriculture and leads to increased use of more and more toxic pesticides. In addition, resistance in one of the "sectors" mentioned above can "crossover" to become problematic in another. Growing pesticide resistance often leads to an increase in chemical inputs to control pests. Exposure to permethrin already has implications for human health, including cancer, endocrine (hormone) disruption, reproductive dysfunction, neurotoxicity, and kidney/liver damage. Mosquito resistance can lead to the increased use of chemical control methods, including the addition of toxic synergists like piperonyl butoxide (PBO), known to cause and exacerbate adverse health effects from exposure. Therefore, researchers need to understand the mechanisms prompting pesticide resistance among mosquito populations to safeguard human health from disease.

The use of permethrin and deltamethrin through fogging and aerial application plays a significant role in the high intensity of resistance among the *Ae. aegypti* colonies from Dhaka. The study highlights that pyrethroids act on the nervous system of insects, using a "knockdown" effect to cause death. Although this study suggests mosquitoes can recover from the knockdown (KD) effect via a mutation in the kdr alleles, this KD effect is dose-dependent. Thus, pyrethroid increases the frequency of kdr mutation to prompt resistance. The study highlights, "[…] the substantial recovery seen after KD suggests poor binding of the pyrethroid to the mutated VGSC and a key role for metabolic mechanisms in 'mopping up' the pyrethroids."

This study is not the first to demonstrate metabolic mechanisms driving genetic resistance among mosquito populations. A Colorado State University study finds two types of pyrethroid resistance: VGSC and detoxification metabolism. Similar to this study, the Colorado researchers suggest mosquitoes who recover from the initial insecticide knockdown contribute to resistance in the field. Sublethal exposure may be responsible for the mosquito's ability to recover. Rather than dying from dehydration and predation, recovery mechanisms allow mosquitoes to develop resistance over time. This study enables researchers to fully understand the genetic differences between mosquitoes who exhibit resistance and those who recover or die. Knowing how genes factor into pesticide metabolism can help researchers understand how resistance evolves under field-realistic conditions. Therefore, it is essential to understand insect behavior that increases vector-borne disease transmission, exacerbating the widespread public health crisis.

In the context of deadly pesticide use in developing countries, Jay Feldman, executive director of Beyond Pesticides, has noted, "We should be advocating for a just world where we no longer treat poverty and development with poisonous band-aids but join together to address the root causes of insect-borne disease because the chemical-dependent alternatives are ultimately deadly for everyone." He also said, "We should focus on the deplorable living conditions and inequitable distribution of wealth and resources worldwide that give rise to squalor, inhumane living conditions, and the poor state of development that, together, breed insect-borne diseases like malaria."

Even if dengue is not a local concern, there remains general concern surrounding the diseases mosquitoes can transmit, including the West Nile and Zika viruses. Beyond Pesticides provides valuable information on mosquito management and insect-borne diseases in the Mosquito Management and Insect-Borne Diseases section devoted to these issues. Keep up on pesticide-related science and news, including mosquitoes and pesticide resistance, on Beyond Pesticides' *Daily News*.

SOURCE: Hasan Mohammad Al-Amin, et al., Insecticide resistance compromises the control of *Aedes aegypti* in Bangladesh, Pest Management Science, 2023;79: 2846–2861.

RESISTANCE | OCTOBER 17, 2023

Paris's Worrying Bed Bug Surge Linked to Insecticide-Resistance

In the past month, Paris, France has witnessed a surge in bed bug populations. From public transportation to hotels, hostels, and movie theatres, bed bugs are posing a threat to the city's two million residents and potentially a broader global population as the infestation spreads.

This resurgence of bed bugs in Paris is not unique. For centuries, these pests have been both adaptable and persistent, presenting an enduring challenge to pest control. However, the current surge in bed bug infestations is not merely a revival of a longstanding problem; it is a complex issue intertwined with the development of resistance to insecticides, mainly through a mechanism known as knockdown resistance. This mechanism, along with three other main resistance mechanisms, has enabled these insects to defy chemical-intensive control methods. Knockdown resistance is a significant factor contributing to the resistance exhibited by bed bugs to insecticides, especially pyrethroids. The mechanism plays a central role in countering the action of these insecticides, which target the nervous system of bed bugs, causing paralysis and eventual death. Knockdown resistance provides the genetic adaptation that provides bed bug populations with resistance to insecticides, inhibiting the effectiveness of certain insecticides. Bed bugs with the mutation have a genetic advantage that allows them to survive exposure to these chemicals.

Insecticides have been utilized to quell bed bug populations for over a century, with DDT initially used to combat these pests before the 1950s. By 1956, the effectiveness of DDT in controlling bed bug populations began to diminish, as the insects developed resistance to the once-potent chemical. The repetitive exposure of bed bugs to DDT led to the survival of bed bugs with genetic mutations that allowed them to survive DDT exposure, giving rise to newer generations with the same mutations.

The banning of DDT in 1972 compelled the United States to turn to organophosphates and, more recently, the commonly used pyrethroids—synthetic insecticides widely used for residential pests. However, there was an unforeseen consequence of DDT resistance: bed bugs with DDT resistance demonstrated resistance to other pesticides, including pyrethroids, even if they had never encountered pyrethroids. This phenomenon, known as cross-resistance, paved the way for a global resurgence of bed bugs and posed challenges for pest control worldwide.

Knockdown resistance is linked to the voltage-gated sodium channels (VGSC) within a bed bug's nervous system. These channels serve as conduits for transmitting electrical signals, enabling nerve cells to communicate and control the bug's movements. Knockdown resistance arises from mutations within the VGSC gene.

Scientists have identified three specific mutations in the common bed bug, *Cimex lectularius:* V419L, L925I, and 1936F. In modifying the function of sodium channels, these mutations make the insect less responsive to the effects of pyrethroid insecticides. As a result, the nerve cells of resistant bed bugs can continue to function despite exposure to these chemicals.

Research has revealed that knockdown resistance is prevalent in bed bug populations, particularly those closely linked to human environments. Most bed bug populations associated with human environments exhibit the L925I mutation, which equips them with resistance to pyrethroids.

This widespread distribution of knockdown resistance raises concerns about the continued use and efficacy of pyrethroids in treating infestations. Bed bugs with knockdown mutations possess the capacity to withstand exposure to insecticides, reducing the effectiveness of these treatments. As a result, infestations persist, inflicting discomfort, economic burdens, and health concerns upon those affected.

Moreover, bed bug resistance to insecticides has extended to new classes of insecticides. The developing resistance of bed bugs to neonicotinoid insecticides raises similar questions about chemical-dependent control strategies for infestations. Research has found that neonicotinoids, once thought by the pest control industry to be the silver bullet solution for bed bug infestations, are losing their efficacy as bed bugs from different regions are becoming resistant to them.

In a study led by Alvaro Romero, PhD and Troy Anderson, PhD, bed bugs collected from homes in Cincinnati and Michigan were exposed to four different neonicotinoids: acetamiprid, dinotefuran, imidacloprid, and thiamethoxam. The study also tested these neonicotinoids on bed bugs that had never been exposed to insecticides. They found that bed bugs previously exposed to neonicotinoids show higher levels of resistance to these insecticides, when compared to the levels of resistance exhibited by the bed bugs that had never been exposed to the neonicotinoids. It took over a thousand times more acetamiprid to kill half of the bed bug population with prior exposure to neonicotinoids, as opposed to the population that had never been exposed to neonicotinoids. This means the bed bugs in the Michigan and Cincinnati study proved to be hundreds or even thousands of times more resistant to neonicotinoids compared to the lab control group.

As insecticide usage continues in response to growing issues of invasive species migration and insect infestations, the infestation problem will only grow worse. The situation in Paris is just one example of what is to come if pesticide dependency continues. The best method for handling infestations is by skipping the chemicals and following a defined integrated pest management system that prioritizes ecologically balanced solutions, and only allows organic-compatible products.

SOURCE: Ondřej Balvín and Warren Booth, Distribution and Frequency of Pyrethroid Resistance-Associated Mutations in Host Lineages of the Bed Bug (Hemiptera: Cimicidae) Across Europe, *Journal of Medical Entomology,* Volume 55, Issue 4, July 2018, Pages 923–928, https://doi.org/10.1093/jme/tjy023.

MORE ON THIS SUBJECT **Regulators Ignore Mosquito Resistance to Pesticides, Promoting Disease Transmission**—August 7, 2023

RESISTANCE | OCTOBER 30, 2023

Despite a Beetle's History of Resistance to Insecticides, EPA Is Pushing Genetically Engineered Pesticide

It is said that the definition of insanity is doing the same thing over and over again and expecting a different result. And so it goes with the U.S. Environmental Protection Agency's (EPA) proposal to register a new genetically engineered pesticide for the Colorado Potato Beetle (CPB); this time with a pesticide that has not been fully evaluated for its adverse effects to people and the environment.

> **The Colorado potato beetle has been dubbed the billion-dollar-bug because of the investment in failed attempts of chemical manufacturers to control the insect, the profits generated by chemical companies despite this failure, and the resulting losses for chemical-intensive farmers.**

Chemical-intensive agriculture has failed to control CPB since resistance to DDT was identified in 1952 and has continued with every family of pesticides since then. CPB has been dubbed the billion-dollar-bug because of the investment in failed attempts of chemical manufacturers to control the insect, the profits generated by chemical companies despite this failure, and the resulting losses for chemical-intensive farmers—not to mention government expenditures for the registration of chemicals that have short efficacy, pollution costs associated with chemical production and use, and lost ecosystem services. But EPA is at it again, registering a new novel pesticide active ingredient, Ledprona, which raises the stakes on potential harm. The only winners in this ongoing failure are the chemical

manufacturers that continue to reap huge economic benefits from the sale of their highly toxic pesticides.

Meanwhile, according to research published in Molecular Biology and Evolution (2022) and hundreds of other scientific articles over the years, "This is the case with insect "super-pests," which repeatedly evolve insecticide resistance even as they are faced with completely novel insecticides, thus perpetuating the arms race that defines the pesticide treadmill." And yet EPA is still at it, despite the success of alternative strategies with organic management systems.

While researchers and the chemical industry keep trying to develop new "silver-bullet" chemicals for controlling CPB, EPA has ignored methods of agricultural management that work without reliance on toxic chemicals. Environmental advocates say that this newest proposed pesticide exemplifies the worst of EPA's pesticide registration program, governed by its Office of Pesticide Programs, because there are alternative methods and the risks of Ledprona have not been found to be "reasonable"—under a weak federal pesticide law, the *Federal Insecticide, Fungicide, and Rodenticide Act* (FIFRA).

The University of Minnesota Extension, in its publication "Organic management recommendations for Colorado potato beetle," describes the range of methods that are integrated into an organic systems approach not reliant on pesticides. It includes crop rotation, early maturing varieties, mulching systems and habitat for natural enemies like ladybugs and parasitic wasps, trapping, and a naturally occurring soil bacterium.

FIFRA requires that EPA register a pesticide only if it determines that the pesticide "will perform its intended function without unreasonable adverse effects on the environment." EPA admits that it is basing its proposed registration decision solely on data the registrant GreenLight Biosciences submitted to fulfill requirements for its prior application for an experimental use permit (EUP), without any additional data. However, there are far fewer data requirements for approval of an EUP than are required for a full registration.

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Ledprona's use of RNAi makes it unique and unlike any other insecticide sprayed on fields. The use of new technology makes it especially imperative to examine all required data for any potential unintended consequences. Since these novel pesticides may be applied by plane, EPA should thoroughly assess the real-world impacts of pesticide drift. This technology, which penetrates plant tissues and leaves traces in the soil, can cause widespread indiscriminate poisoning—as has been seen with bees, butterflies, birds, and the larger catastrophic decline of insect populations, called the "insect apocalypse." The effects, especially on threatened and endangered species like the American burying beetle, Hungerford's crawling water beetle, the Northeastern beach tiger beetle, and the Puritan tiger beetle, must be evaluated. These species are found near potato production areas close to where the Experimental Trials were being conducted and could be direct casualties of this new biopesticide.

It should be noted that the EPA's definition of "biopesticide" is broad and includes genetically engineered organisms. EPA says, "Biopesticides are certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals. . . . Biopesticides include naturally occurring substances that control pests (biochemical pesticides), microorganisms that control pests (microbial pesticides), and pesticidal substances produced by plants containing added genetic material (plant-incorporated protectants) or PIPs."

In addition, researchers from the U.S. and Switzerland have published findings, a beginning assessment of how the use of this new category of pesticides—RNAi, delivered in double-stranded RNA (dsRNA) molecules—might impact soils and nontarget microorganisms in the soil. The coauthors (Kimberly M. Parker, PhD, et al.) note that, "The ecological risk assessment of these emerging pesticides necessitates an understanding of the fate of dsRNA molecules in receiving environments, among which agricultural soils are most important." Their research has continued, finding that "Due to the ability of DOM (dissolved organic matter) to both bind and suppress the enzymatic degradation of RNA, RNA biodegradation may be slowed in environmental systems with high DOM concentrations, which may increase its persistence."

SOURCES: Benjamin Pélissié, et al., Genome Resequencing Reveals Rapid, Repeated Evolution in the Colorado Potato Beetle, *Molecular Biology and Evolution,* Volume 39, Issue 2, February 2022, msac016, https://doi.org/10.1093/molbev/msac016.

MORE ON THIS SUBJECT

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Pollution-Associated Liver Disease with Sex-Specific Effects Linked to Persistent Legacy Insecticide, Chlordane—October 4, 2023

Insecticide-Resistant Mosquito Sets Africa's Malaria Fight Back to Square One—October 10, 2023

RESISTANCE | OCTOBER 27, 2023

EPA To Allow Genetically-Based Pesticides, Incomplete Testing, and Documented Adverse Effects

In a predictable move, EPA proposes to greenlight a type of genetic engineering to solve a problem created by the industrial paradigm for pest control, i.e. vast acreages of monoculture treated with millions of tons of toxic pesticides leading to rapid resistance among crop pests. In this case EPA wants to approve using a nucleic acid—double-stranded RNA (dsRNA)–called "interfering RNA," or RNAi—to silence a gene crucial to the survival of the Colorado Potato Beetle (CPB), the scourge of potato farmers around the world. But EPA has skipped over important steps in its decision-making process and rushed to judgment.

Like chemical pesticides, genetically-based pesticides are regulated under the *Federal Insecticide, Fungicide, and Rodenticide Act* (FIFRA). In 2020, Massachusetts-based GreenLight Biosciences applied for registration of its RNAi active ingredient, Ledprona, and its end-use product, Calantha. The company executive heading the effort is an alumnus of Monsanto and several other major chemical companies. Last May EPA, granted GreenLight an Experimental Use Permit (EUP) authorizing field studies in states that produce tons of potatoes. A mere five months later, EPA announced its decision to approve the registration based almost entirely on incomplete EUP data and giving the public very little time to comment.

Formally titled "Colorado Potato Beetle (CPB)-specific recombinant double-stranded interfering Oligonucleotide GS2 *Leptinotarsa decemlineata,*" Ledprona disrupts an RNA process inside cells to block expression of a particular CPB gene. This prevents the gene from specifying an important protein. When a CPB ingests Ledprona on a potato leaf, the RNAi nucleotide spreads into the cells of the beetle's gut. The cells die, which shortly kills the beetle.

Unfortunately, dsRNA molecules may wander from their intended targets. Inside a cell, the long dsRNA strand gets clipped into small pieces called siRNAs ("small interfering RNAs"), whose configuration may also align with many other sections of a genome and affect nontarget genes, with entirely different effects. One experiment with interfering RNA found complete matches in 17 percent of off-target sequences. Neither EPA nor Greenlight has addressed this risk.

According to EPA's Environmental Risk Assessment (ERA), Greenlight intends Calantha to be applied in ground spray, aerial spray, and in irrigation water—in other words, very broadly, and in a manner that will inevitably entail some spray drift.

The Center for Food Safety (CFS) prepared a blistering comment to EPA noting the agency's extreme disregard for both known biological processes and the unknowns of losing a novel piece of cellular machinery into the

wild. According to the CFS, the EUP field trials granted to Greenlight remain incomplete and will not expire until April 30, 2025, yet EPA admits that its approval of Ledprona and Calantha relies solely on data Greenlight submitted with its application for the EUP–whose data requirements are considerably lower than those for new use approvals. FIFRA requires, for example, data on toxicity to fish, birds, and plants. GreenLight has not provided that data so far.

EPA assumes that only organisms that resemble the CPB might be susceptible to Ledprona's interference with their cellular machinery. EPA states that "there is a reasonable expectation of no discernible effects to occur to any non-coleopteran nontarget organisms exposed to Ledprona. . . . EPA analysis also examined the 19 federally listed threatened and endangered ('listed') beetle species and determined that no exposure is expected for 15 of the 19 federally listed threatened and endangered ('listed') beetle species from a section 3 registration of Calantha containing Ledprona." (The CPB, in the order Coleoptera along with 400,000 other beetle species known to science. Many coleopterans provide beneficial services.)

We can expect more pesticide products to be based on genetic processes such as RNAi's regulation of gene expression as farmers and chemical companies get more desperate with each passing report of pests' ability to evade pesticides. It is unsurprising that the CPB is an early target because it is notorious for its rapid development of resistance.

Additionally, EPA says, "Physiological barriers are present within vertebrate species that prevent the dsRNA such as Ledprona from reaching and penetrating the gut in vertebrate species." Given the unpredictable alignments of the small interfering RNAs in a genome, this too is an iffy assumption. The CFS comment notes that, although EPA has not provided any information to the public about Ledprona's nucleotide length, that data is an important factor in assessing the product's potential toxicity. EPA has designated the dsRNA in Ledprona as "non-coding," which it takes to mean that it would not function in a human body, but, in fact, nobody knows whether or how many such "long, non-coding RNAs" function in many species. What *is* known, according to CFS, is that human innate immune systems respond to such sequences, which often come from viruses or from the body's own damaged cells, with inflammation.

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In the long run CPB will win. It is already ahead. In 2021, a research team, three of whom are employed by Monsanto, found that CPB "can develop high levels of resistance against insecticidal dsRNA" when the dsRNA is applied to leaves. The study also found that the dsRNA affected more than one gene. Various analyses of

CPB's response to a range of doses led the scientists to conclude that, after a few generations, resistance to dsRNA reached 11,100 times that of the founding generation of beetles. The researchers attributed CPB's virtuosic ability to resist pesticides partly to the beetle's highly flexible and transposable genetic elements. This indicates that creating precise and effective products using genetics is fraught with risks. A plain hydrocarbon molecule is understood vastly better than the interplay of the trillions of genes in the world.

Pesticide resistance was first noted in 1914, but the industry still fails to recognize that it cannot bet against the house. To cope with the inevitable triumph of natural selection, pesticide manufacturers are promoting the use of dsRNA products in combination with traditional pesticides, with the idea that their mechanisms of action will alternate and prevent pests from adapting. Combining pesticides with RNA interference can be framed as part of "integrated pest management," although as a 2018 review in *Science* noted, the notion that "such combinations will slow [the development of] resistance is theoretically controversial and lacks empirical support."

Beyond Pesticides chronicled in 2019 the promotion of interfering dsRNA technologies by pesticide companies despite the recognition that their effects on nontarget organisms cannot be predicted.

"With the allowance of gene-manipulating RNAi pesticides, EPA is repeating a pattern of allowing uncertainty that has historically resulted in serious unexpected and uncontrolled hazards, despite the availability of organic practices and products that are currently available," said Beyond Pesticides' executive director, Jay Feldman. Mr. Feldman continued: "The agency has failed to fully evaluate the fate of genetic material and its degradation products on nontarget species and the likely potential for indiscriminate poisoning. We are calling for a moratorium on RNAi pesticides until these questions can be fully answered."

An expert at another federal agency once observed that it is not a good idea to rely on "a conclusion drawn from a consensus" rather than from empirical evidence when making important decisions. In this case, EPA has done exactly that, mistaking suppositions for facts. EPA's decision rests on a foundation of uncertain assumptions, many of which are implicit in EPA's evaluation rather than explicitly enumerated, and whose reliability EPA did not examine.

SOURCES:

EPA Opens Public Comment Period on Proposal to Register Novel Pesticide Technology for Potato Crops, https://www.epa.gov/pesticides/epa-opens-public-comment-period-proposal-register-novel-pesticide-technology-potato

Environmental Risk Assessment for a FIFRA Section 3 Registration of the New Product GS2 Formulation (Calantha) Containing Ledprona, https://www.regulations.gov/document/EPA-HQ-OPP-2021-0271-0006

Human Health Risk Assessment, Review of Product Characterization and Manufacturing Process for the New end-use product, Calantha Human Health Risk Assessment, Review of Product Characterization and Manufacturing Process for the New end-use product, Calantha, https://www.regulations.gov/document/EPA-HQ-OPP-2021-0271-0005

POLICY | JANUARY 24, 2023

Legal Case Opens To Stop Antibiotics in Citrus and Advance Organic, Given Resistant Bacteria Crisis

[*Eds note: update on court decision—Litigation successfully stopped antibiotic use in Florida citrus in December 2023. However, the decision was reached on EPA failure to comply with the Endangered Species Act not on the issue of antibiotic resistance. Despite the scientific literature on horizontal gene transfer (movement of genes in bacteria from one bacterial species to another) through agricultural use of pesticides, the court found, "EPA emphasized that "there is no data that antibiotic use in agriculture leads to the presence of antibiotic resistance in bacteria of human health concern," and that "[a]t the present time, there is little evidence for or against the presence of microbes of human health concern in the plant agricultural environment." And yet, on May 19, 2019, The New York Times reported, "The agency approved the expanded use despite strenuous objections from the Food and Drug Administration and the Centers for Disease Control and Prevention, which warn that the heavy use of antimicrobial drugs in agriculture could spur germs to mutate so they become resistant to the drugs, threatening the lives of millions of people."*]

Oral arguments began in January in a lawsuit challenging the U.S. Environmental Protection Agency's (EPA) approval of the antibiotic streptomycin as a pesticide on citrus crops. Brought forth by a coalition of farmworker, health, and environmental groups, the lawsuit aims to stop the use of a critical medical treatment for agricultural purposes. "Humanity's dwindling supply of medically effective antibiotics is not worth sacrificing for an industry that has safer alternatives avail-able," said Drew Toher, former community resource and policy director at Beyond Pesticides. "Despite the challenges, we know from the elimination of this material in organic production that we don't need antibiotics in order to produce a glass of orange juice."

In 2020, *The Lancet* published an article that identifies several of the

multiple and interacting crises the U.S. and world face, with a focus on another "looming potential pandemic . . . [a] rise in multidrug-resistant bacterial infections that are undetected, undiagnosed, and increasingly untreatable, [whose rise] threatens the health of people in the USA and globally." It calls on leaders in the U.S. and beyond, asking that even as they address the current coronavirus pandemic, they also attend to the antimicrobial resistance (AMR) problem, which is a growing threat to public health. The coauthors outline a number of strategies for progress on AMR, including banning of medically important antibiotics in agribusiness, and promoting consumer, and supplier and private sector, awareness and action on food choices.

The growing threat of antibiotic resistance is a major health care issue. Beyond Pesticides has written, "Many bacterial infections are becoming resistant to the most commonly prescribed antibiotics, resulting in longer-lasting infections, higher medical expenses, the need for more costly or hazardous medications, and the inability to treat life-threatening infections. The development and spread of antibiotic resistance is the inevitable effect of antibiotic use. Bacteria evolve quickly, and antibiotics provide strong selection pressure for those strains with genes for resistance."

EPA registered streptomycin as a tool for citrus growers because it can suppress Huanglongbing (HLB) disease, also known as citrus greening, caused by a bacterial pathogen transmitted by the invasive Asian citrus psyllid. HLB results in citrus fruit becoming green, misshapen, and bitter. The agency also claims streptomycin "will aid resistance management" for citrus canker disease, a contagious pathogen that can be spread by wind, rain and human activity. Once infected, citrus canker is incurable. Growers may use copper pesticides to delay the inevitable, but there is growing concern of resistance to copper compounds.

Data show that over 35,000 Americans die each year because of antibiotic resistant bacteria. And antibiotic-based pesticides present a significant risk to endangered animals in citrus growing regions, like Florida panthers and Joaquin kit foxes, in addition to dwindling pollinator populations.

While both diseases represent legitimate concerns for the citrus industry, it is clear that the answer cannot be to take an important human medical treatment and broadcast spray hundreds of thousands of pounds across upwards of 650,000 acres of U.S. cropland. EPA's shortsighted response may help the industry in the short term, but most of these benefits will be seen not by farmers but top-level executives, with the long-term risk of exacerbating the pre-existing epidemic of antibiotic resistance.

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The health risk of this decision is greatest to the essential workers who manage citrus groves. "The use of streptomycin as a pesticide continues to be an ongoing threat to the health and safety of our farmworkers, who are at the frontlines of feeding our nation," said Jeannie Economos, coordinator of the Pesticide Safety and Environmental Health Program at Farmworker Association of Florida. "We're urging swift resolution of this case and an end to the misuse of medically important antibiotics within our food systems. Every day of delay means more farmworkers are exposed, putting themselves and their families at risk."

The lawsuit against EPA's decision includes Beyond Pesticides, U.S. Public Interest Research Group, Environment Confederation of Southwest Florida, Farmworker Association of Florida, Farmworker Justice, Migrant Clinicians Network, represented by Natural Resources Defense Council, Earthjustice, and Center for Biological Diversity. Petitioners argue that EPA failed to ensure that the approved uses of streptomycin as a pesticide would not result in unreasonable adverse effects on human health or the environment, and say that EPA failed to adequately assess risks streptomycin poses to endangered species.

EPA's decision puts it at odds with other agencies, as officials with both the Centers for Disease Control and Prevention and the Food and Drug Administration have raised concerns about using medically important antibiotics as pesticides.

Concerns over turning medical treatments into pesticides are not conjecture but borne out of experiences already concerning on the ground. There is significant evidence available now that widespread use of human-important antifungal drugs as antibiotics is resulting in resistance to dangerous fungal pathogens that are now infecting humans. *Aspergillus fumigatus*, a common mold found in soils and composts, has become increasingly virulent to humans.

Between 2000 and 2013, cases of invasive aspergillosis increased 3 percent per annum, and roughly 300,000 worldwide are diagnosed each year. Data show that roughly 20 percent of *Aspergillus fumigatus* samples are resistant to azole fungicides used in agriculture, but also critical for human treatments.

Concerns over turning medical treatments into pesticides are not conjecture but borne out of experiences already concerning on the ground. There is significant evidence available now that widespread use of human-important antifungal drugs as antibiotics is resulting in resistance to dangerous fungal pathogens that are now infecting humans.

By finding evidence that the same infections strains of *Aspergillus fumigatus* were also resistant to non-azole agricultural fungicides, scientists provided a direct link from hospital infections to on-farm fungicide applications. In the same vein, the emerging fungal pathogen *Candida auris* displays 90 percent of infections resistant to one drug, and 30 percent to two or more, with this resistance tracing back to farm use.

Nearly 10 years ago, Beyond Pesticides' galvanized action on the National Organic Standards Board to eliminate the use of antibiotics like streptomycin in organic apple and pear production. At issue was the destructive bacterial disease fire blight, which can turn blossoms, leaves, twigs, and branches of affected trees black, having the appearance of being hit by fire. Despite the challenges, farmers were able to transition to resistant varieties and craft system management plans to better address outbreaks without resorting to antibiotic use.

Unlike the challenge to organic apple and pear growers, chemical-based citrus farmers already have proof of concept that citrus crops can be grown to market without the use of medically important antibiotics. Organic citrus farmers are prohibited from employing not only antibiotics, but other toxic pesticides such as the systemic neonicotinoids that are often used on chemical-intensive farm operations. Organic growers like Uncle Matt's in Florida discuss the importance of breeding programs for tolerant rootstock, the use of botanical insecticides such as neem and clove oil, and the release of the biological control agent Tamarixia wasps, which feed on Asian Citrus Psyllids. Watch Uncle Matt's Benny McClean, production manager, speak about organic citrus production in Florida at Beyond Pesticide's 33rd National Pesticide Forum.

While the organic approach shows the wisdom and value of organic's drive toward "continuous improvement," EPA's response to industry executives crowing about the potential for declining profit margins represents a short-sighted, knee-jerk reaction. There is no need to steal from our health future to protect the inability of the citrus industry to responsibly manage its problems; what's needed is a strategy that represents a long-term investment in the future of citrus production. Rather than bringing new chemicals to the market, environmental advocates urge EPA to work with growers and the U.S. Department of Agriculture to deploy resistant rootstocks, new biologicals, and truly least-toxic pesticides.

SOURCE: U.S. Court of Appeals, Migrant Clinicians Network, Beyond Pesticides, et al., Case: 21-70719, 12/13/2023, ID: 12836809, 2023; Steffanie Strathdee, et al., Confronting antimicrobial resistance beyond the COVID-19 pandemic and the 2020 election, *The Lancet*, September 20, 2020, https://doi.org/10.1016/S0140-6736(20)32063-8.

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