

Congress of the United States
Washington, DC 20510

August 28, 2019

Andrew R. Wheeler
Administrator
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20004

Dear Administrator Wheeler,

We write with serious concerns regarding the Environmental Protection Agency's (EPA) final decision to expand the use of the antibiotic oxytetracycline and proposed decision to expand the use of the antibiotic streptomycin as pesticides for citrus production.¹ EPA appears to have pursued these proposals despite warnings from the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) that massive agricultural use of these crucial, life-saving antibiotics could spur antimicrobial resistance and create unreasonably high risks to human health. Given these serious public health risks and the scientific evidence indicating that additional agricultural use of these pesticides will increase those risks,² we urge you to reconsider these decisions. Additionally, we request information regarding EPA's decision-making process.

Antimicrobial Resistance Is an Urgent Public Health Crisis

Antibiotics are critically important medicines used to treat infections and ensure the safety and efficacy of medical procedures. Streptomycin is considered "critically important" and oxytetracycline is considered "highly important" to human health by the World Health Organization. Both are used to treat many hard-to-treat diseases such as syphilis, tuberculosis, chlamydia, and urinary tract infections.³ However, the overuse and misuse of antibiotics can, through the process of natural selection, result in new strains of drug-resistant "superbugs."⁴

¹ [Streptomycin- tolerance for use in/on citrus fruit \(Crop Group 10-10\) and citrus, dried pulp](#), Docket ID: EPA-HQ-OPP-2016-0067; [Oxytetracycline Calcium- Pesticide Petition to establish tolerances for use on Fruit, Citus, Crop Group 10-10 and Citrus, Dried Pulp](#), Docket ID: EPA-HQ-OPP-2016-0754.

² Centers for Disease Control and Prevention, *Antimicrobial Susceptibility Testing of Human Bacterial Pathogens to Antibiotics Used as Pesticides: Report to EPA* (May 11, 2017), http://www.biologicaldiversity.org/campaigns/pesticides_reduction/pdfs/CDC-study-from-FOIA.pdf.

³ World Health Organization, *Critically Important Antimicrobials for Human Medicine* (6th Rev. 2018), apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf?ua=1.

⁴ World Health Organization, *Antibiotic Resistance Fact Sheet* (2018), www.who.int/news-room/fact-sheets/detail/antibiotic-resistance ("Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance."); Ventola, *The Antibiotic Resistance Crisis; Part 1: Causes and Threats*, 40(4) *Pharmacy & Therapeutics* 277 (2015); Matt Richtei & Andrew Jacobs, *A Mysterious Infection, Spanning the Globe*

When this occurs, bacterial infections that should be easily treatable with antibiotics instead fail to respond to first- and second-line antibiotic treatments, and in some cases can become resistant to virtually all available antibiotics.

The result is a looming public health crisis. CDC estimates that in the United States, more than two million people are infected with antibiotic-resistant organisms every year, and 23,000 die as a result.⁵ Health experts warn the problem will continue to grow unless we drastically reduce unnecessary antibiotic use. A recent report found that without swift action, 10 million people worldwide could die each year by 2050 from drug-resistant infections.⁶

EPA's Decisions Will Result in an Unprecedented Expansion of Use of Antibiotics as Pesticides

In December 2018, EPA issued a proposed approval for streptomycin and final approval for oxytetracycline for expanded use on citrus orchards to treat the citrus greening outbreak.⁷ The volume of new uses would be unprecedented—the largest-ever plant agricultural use of antibiotics ever authorized in the United States. The approvals would allow agribusinesses to spray more than 650,000 pounds of streptomycin on citrus trees every year, over **40 times as much** as is used in the United States each year to treat human disease.⁸ The final approval for oxytetracycline will allow use of 388,000 pounds per year; 130,000 pounds more than all tetracyclines used in the United States annually for human medicine.⁹

EPA Ignored Scientific Evidence Demonstrating Pesticidal Use May Increase Risk of Antimicrobial Resistance

In its decisions regarding the uses of streptomycin and oxytetracycline as pesticides, EPA has acknowledged that “[a]ntibiotic resistance is a growing public health concern in the United

in a Climate of Secrecy, N.Y. Times, Apr. 6, 2019, www.nytimes.com/2019/04/06/health/drug-resistant-candida-auris.html.

⁵ Centers for Disease Control and Prevention, *The Core Elements of Hospital Antibiotic Stewardship Protection*, www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. Some estimates are as high as 162,000 deaths per year. Burnham, Olsen, & Kollef, “Re-estimating annual deaths due to multidrug-resistant organism infections,” *Infection Control & Hospital Epidemiology*, 40(1) (2019), 112-113.

⁶ The Review on Antimicrobial Resistance, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, at p. 20 (May 2016), amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf.

⁷ EPA, Section 3 Proposed New Use of Streptomycin Sulfate on Citrus, Crop Group 10-10 (Dec. 21, 2018), www.regulations.gov/document?D=EPA-HQ-OPP-2016-0067-0006; EPA, Final Registration Decision for the New Use of the Active Ingredient Oxytetracycline Hydrochloride on Citrus Crop Group 10-10 (Dec. 7, 2018), www.regulations.gov/document?D=EPA-HQ-OPP-2015-0820-0031.

⁸ Center for Biological Diversity, “Comments Opposing EPA’s Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10 (Docket # EPA-HQ-OPP-2016-0067; EPA Reg. No. 71185-4, 80990-3, 80990-4),” at p. 2 (Jan. 18, 2019), www.biologicaldiversity.org/campaigns/pesticides_reduction/pdfs/Streptomycin-Comments.pdf.

⁹ N. Donley, “The USA lags behind other agricultural nations in banning harmful pesticides,” *Environmental Health*, Vol. 18, p. 44 (2019), www.ncbi.nlm.nih.gov/pmc/articles/PMC6555703/.

States and abroad” and “[r]esistance occurs when bacteria adapt to the antibiotics designed to kill them, making the antibiotics less effective.”¹⁰ Yet, EPA appears to have ignored scientific evidence that demonstrates pesticidal use may increase the risk of antimicrobial resistance.

To start, EPA downplayed and ignored concerns outlined in a report CDC submitted to EPA in 2018,¹¹ which found that using streptomycin and oxytetracycline as pesticides “has the potential to select for antimicrobial resistant bacteria present in the environment.”¹² CDC’s research shows that spraying antibiotics on citrus trees could contribute significantly to the development of drug-resistant bacteria. Those resistant bacteria could eventually make contact with humans and afflict them with infections that will be difficult, and potentially impossible, to treat.

This is not the first instance of CDC raising concerns with EPA over the use of streptomycin and oxytetracycline as pesticides. CDC’s concerns date back over 20 years, as evidenced by letters of opposition CDC sent to EPA regarding the use of gentamicin sulfate in apple orchards. In an October 8, 1998 letter to an Assistant EPA Administrator, CDC wrote, “CDC believes that pesticidal uses of antimicrobial drugs such as streptomycin and oxytetracycline should follow the World Health Organization’s recommendations on the subtherapeutic use of antimicrobial drugs in food animals: antimicrobial drugs which are used in human medicine or which select for resistance to drugs used in human medicine, should not be used for subtherapeutic purposes.”¹³

EPA also appears to have ignored recommendations from its own experts who conducted a risk analysis of the drugs’ use as pesticides. Because there is no existing framework for assessing antimicrobial resistance specifically caused by antibiotic use on citrus, EPA modeled its risk analysis off of FDA’s Guidance for Industry #152, which outlines “a recommended approach for assessing the safety of” new animal antimicrobials “with regard to their microbiological effects on bacteria of human health concern.”¹⁴ In doing so, EPA found that the proposed uses of streptomycin and oxytetracycline created a risk of antimicrobial resistance for humans. However, after determining this, EPA failed to follow FDA’s recommended standard for approval outlined in the Guidance for Industry #152, which advises not to approve an antibiotic use with even a moderate risk to human health unless there is “reasonable certainty of no harm to human health”

¹⁰ EPA, *Streptomycin: Proposed Interim Registration Review Decision: Case Number 0169* (Dec. 27, 2018), Docket No. EPA-HQ-OPP-2008-0687, at p. 14 and p.17 (“*Streptomycin Interim Decision*”), www.regulations.gov/document?D=EPA-HQ-OPP-2008-0687-0024; EPA, *Oxytetracycline: Proposed Interim Registration Review Decision: Case Number 0655* (Dec. 17, 2018), Docket No. EPA-HQ-OPP-2008-0686, at p. 17 and p. 15 (“*Oxytetracycline Proposed Interim Decision*”), www.regulations.gov/document?D=EPA-HQ-OPP-2008-0686-0027.

¹¹ The EPA stated that, in consultation with other federal agencies including CDC, it could only “conclude[] that such risk [of antimicrobial resistance of human pathogens] is possible and its probability is unknown at present.” *Streptomycin Interim Decision* at p. 19; *Oxytetracycline Proposed Interim Decision* at p. 17.

¹² See note 2 at p. 3.

¹³ Letter from James Hughes, M.D., CDC, to Dr. Lynn R. Goldman, Assistant Administrator, EPA, October 8, 1998, www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2006-0234-0014&attachmentNumber=3&contentType=pdf.

¹⁴ FDA, Guidance for Industry #152, “Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern,” www.fda.gov/media/69949/download.

for that particular use.¹⁵ There is no such certainty here to justify the proposed use in light of the known risks.

Furthermore, EPA experts reviewing antimicrobial risk data recommended that use of oxytetracycline as a pesticide “be contingent on establishing baseline data on oxytetracycline resistance and the presence of bacteria of human health concern in citrus orchards.”¹⁶ A similar recommendation was made by the same EPA experts in their review of the microbiological risk assessment of the use of streptomycin in citrus.¹⁷ EPA, however, approved the use of oxytetracycline without requiring submission of this baseline data,¹⁸ and has proposed approving streptomycin without the recommended baseline data.¹⁹ Both drugs continue to be used on citrus orchards despite the absence of the baseline data: oxytetracycline under the registration and streptomycin under an emergency exemption.

Lastly, EPA experts recommended that EPA implement monitoring plans, which would require pesticide registrants to monitor the development of antimicrobial resistance and submit reports to the agency with their findings. However, the requirements for sampling in the final and proposed registration decisions simply mention monitoring soils and citrus and do not provide specific methodologies or requirements for doing so.

Taken all together, your agency should have sought greater assurances and a better understanding of the human—and environmental²⁰—risks to expanded pesticide use. EPA’s

¹⁵ The EPA borrowed an antimicrobial resistance analysis from the FDA (#152) under which the antimicrobial risk of the proposed uses were “medium,” while FDA’s own guidance requires that antibiotics uses should only be approved for “medium” risks when “FDA can conclude that there is a *reasonable certainty of no harm to human health*.” FDA, Guidance for Industry #152, “Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern,” at p. 24 (emphasis added), www.fda.gov/media/69949/download.

¹⁶ EPA, Review of Geologic/AgroSource’s analysis of oxytetracycline’s safety with regard to its microbiological effect on bacteria of human health concern (FDA/CVM Guidance to Industry #152) for a Section 3 registration on citrus crop group 10-10, at p. 3 (Oct. 25, 2017), www.regulations.gov/document?D=EPA-HQ-OPP-2015-0820-0012.

¹⁷ EPA, Review of AgroSource’s analysis of streptomycin’s safety with regard to its microbiological effect on bacteria of human health concern (FDA/CVM Guidance to Industry #152) for a Section 3 registration on citrus crop group 10-10, at p. 3 (Oct. 25, 2017), <https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0067-0015>.

¹⁸ EPA, Final Registration Decision for the New Use of the Active Ingredient Oxytetracycline Hydrochloride on Citrus Crop Group 10-10 (Nov. 23, 2018), www.regulations.gov/document?D=EPA-HQ-OPP-2015-0820-0031.

¹⁹ EPA, Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10 (Dec. 21, 2018), <https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0067-0023>.

²⁰ In addition to reducing the effectiveness of life-saving medicines, the magnitude of EPA’s proposed antibiotic spraying could cause significant environmental damage to the microbiomes of animals in and around citrus orchards that are sprayed. The potential effect on honeybees and native pollinators is particularly concerning because of their attraction to citrus flowers. Exposure to oxytetracycline and streptomycin could negatively impact the bees’ microbiomes and make them more susceptible to disease. It could also spread antibiotic-resistance genes far and wide as honeybees are shipped around the country to pollinate different crops. See Consumer Reports, “Comments on EPA’s Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10 (Docket # EPA-HQ-OPP-2016-0067; EPA Reg. No. 71185-4, 80990-3, 80990-4)” (March 14,

failure to fully consider these risks is especially troubling in light of the fact that the proposed technique of spraying massive quantities of these antibiotics has never proven to be effective, and indeed has now been shown in a study by citrus researchers at the University of Florida to have no demonstrable effect.²¹ We urge you to reconsider your decisions to approve the agricultural use of streptomycin and oxytetracycline.

Questions & Requests for Documents

The fact that EPA arrived at conclusions that appear to disregard scientific evidence showing significant risks to human health and our environment raises grave concerns that EPA has not appropriately considered all available evidence. Accordingly, we are requesting documents and written answers to the following questions, which will help us better understand and ensure that EPA is fulfilling its mandate to protect the American public from pesticides that pose “any unreasonable risk to man or the environment.”²²

1. EPA’s proposals for oxytetracycline and streptomycin contradict FDA’s Guidance for Industry #152 and CDC’s warnings that subtherapeutic use of antibiotics could increase antimicrobial resistance. How and why does EPA justify ignoring the guidance from FDA and CDC?
2. The organism responsible for citrus greening, *Candidatus Liberibacter asiaticus*, is not culturable, making it difficult to monitor for the emergence of resistance. What requirements will EPA put in place to require pesticide sponsors to monitor for the development of resistance in the target organism? Please provide the protocol for resistance management plans EPA is requiring pesticide makers to submit.
3. Did EPA assess the risk of antimicrobial resistance to workers applying these antibiotics under field conditions? If so, please provide all data and analysis considered, including data or analysis supporting the effectiveness of measures designed to reduce exposure to handlers.
4. CDC, as far back as 1998, has recommended the consideration of impact on non-target organisms and animals in the orchard environment in any application for the use of antibiotics as pesticides. Did EPA assess how its proposals could impact the selection for and spread of resistant bacteria in or on the specific indicator organisms listed below?
 - a. The fruit,
 - b. The trees, including the plant pathogen targets,
 - c. The orchard soil, and
 - d. The animal populations, including honeybees and native pollinators.

2019), <https://advocacy.consumerreports.org/wp-content/uploads/2019/03/CR-comments-on-EPA-approval-of-streptomycin-in-citrus-3.14.19.pdf>.

²¹ Andrew Jacobs, “Spraying Antibiotics to Fight Citrus Scourge Doesn’t Help, Study Finds,” N.Y. Times, August 16, 2019, <https://www.nytimes.com/2019/08/16/health/antibiotics-citrus-spraying.html>.

²² EPA, “Summary of the Federal Insecticide, Fungicide, and Rodenticide Act,” <https://www.epa.gov/laws-regulations/summary-federal-insecticide-fungicide-and-rodenticide-act>.

If so, please provide any and all such data, analysis, and studies.

5. In an attempt to reduce risks of antimicrobial resistance, EPA has proposed restricting the use of oxytetracycline in citrus to two consecutive applications. However, these cycles could potentially be followed by two consecutive applications of streptomycin under an emergency approval or future EPA approval. Biomedical research studies have found cycling between antibiotics to be ineffective in reducing resistance selection in humans.²³ Please provide any evidence EPA used to conclude that this restriction will reduce the risk of antimicrobial resistance.
6. What, if any, alternative measures did EPA consider to reduce the risk of antimicrobial resistance from these products?
 - a. Did EPA consider restricting the use to injection in trees rather than airblast spraying? If so, what evidence did EPA use to conclude airblast spraying was preferred? If not, why not?
 - b. Did EPA consider limiting or restricting the acres or geographical coverage of the proposed use? If so, what evidence did EPA use to reject consideration of geographical restriction? If not, why not?
 - c. Did EPA consider making streptomycin and oxytetracycline a Restricted Use Pesticide to ensure that only a licensed professional pest control operator could apply it? If so, what evidence did EPA use to suggest this measure was not needed? If not, why not?
7. What is EPA doing to close any data gaps identified in questions 2-6?
8. Please provide all written or electronic communication regarding the proposed and final decisions with the following parties:
 - a. The U.S. Food and Drug Administration,
 - b. The U.S. Centers for Disease Control and Prevention,
 - c. The U.S. Department of Agriculture,
 - d. The Office of Management and Budget,
 - e. The White House, and
 - f. AgroSource, Geo Logic Corporation, Nufarm, or any other manufacturer of the agricultural pesticides streptomycin and oxytetracycline.

EPA Should Reconsider Its Proposed and Final Decisions

While citrus greening is a serious concern, EPA's proposals to significantly expand the application of streptomycin and oxytetracycline on citrus will likely exacerbate the problem of antimicrobial resistance. Antibiotics are life-saving medicines and, except in extraordinary

²³ University of Minnesota, Center for Infectious Disease Research and Policy, "Antibiotic cycling, mixing don't affect resistance study says" (Jan. 26, 2018), <http://www.cidrap.umn.edu/news-perspective/2018/01/antibiotic-cycling-mixing-dont-affect-resistance-study-says>.

circumstances, should only be used to treat specific illness in people and animals. EPA's assessments appear to ignore scientific evidence, violate the principle of judicious antibiotic use, and could create unnecessary harm to human health by authorizing an unprecedented amount of medically important antibiotics to be used for plant agriculture.

For the reasons above, we respectfully request that EPA reconsider its proposed and final decisions and not proceed with authorizing the use of streptomycin and oxytetracycline on citrus until a determination has been made that doing so will not exacerbate antimicrobial resistance and harm human health.

Thank you for your attention to this matter. We request written answers and responses to our questions and requests for documents by no later than September 20, 2019.

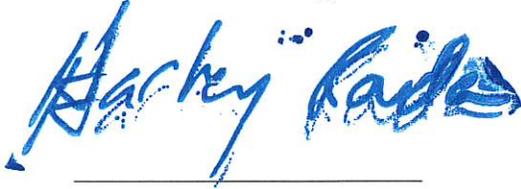
Sincerely,



Jackie Speier
Member of Congress



Elizabeth Warren
United States Senator



Harley Rouda, Chair
Subcommittee on Environment
House Committee on Oversight and Reform



Richard Blumenthal
United States Senator



Raja Krishnamoorthi, Chair
Subcommittee on Economic and Consumer Policy
House Committee on Oversight and Reform



Kirsten Gillibrand
United States Senator



Jan Schakowsky
Member of Congress