CENTER FOR FOOD SAFETY

March 14, 2019

Office of Pesticide Programs Docket
Environmental Protection Agency
Docket Center (EPA/DC) (28221T)
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Re: 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)

The Center for Food Safety requests that you reverse the proposed decision to approve new uses of the active ingredient streptomycin on citrus crop group 10-10. The new uses under consideration are for management of Huanglongbing (HLB), also known as citrus greening, and Xanthomonus citri subsp. Citri (Xcc), the causal agent of citrus canker disease. The Proposed Registration Decision[1] approving the new uses would result in a massive increase in agricultural use of this highly important drug. In the Proposed Registration Decision (PRD), the Environmental Protection Agency (EPA) notes that the "rapidly spreading and devastating nature of HLB makes it plausible that the full label-rate will be used on all affected citrus acreage" and thus the agency uses the total 764,000 acres of citrus crops as the likely affected acreage[2]. This amounts to an area nearly 16 times the area of the District of Columbia, an amazing and irresponsible use medically important antibiotic. Yet, the EPA and the drug registrants recognize that the antibiotic will only suppress not treat the disease[3] and resistance in the target pathogen can't be tested for as the pathogen is not one that can be cultured at present.[4]

EPA estimates that citrus growers will use 1.02 pounds of streptomycin annually per acre (PRD, page 2). Applied to the total U.S. citrus acreage--764,000 acres--this use results in nearly 80,000 pounds per year of active ingredient. EPA reports that 36,000 pounds of streptomycin are used annually on all other crops.[5] , so this approval would result in markedly more streptomycin use in citrus than on all other corps. This amount is 54 times the total of streptomycin and related drugs used in human medicine[6] and 1.4 times the amount used in animals in 2017[7] (FDA, 2018). This violates all standards of careful antimicrobial stewardship.

The risk of increased antimicrobial resistance is especially concerning. EPA's decision runs contrary to efforts by other parts of the US government to reduce antibiotic use in agriculture and human medicine, in order to combat resistance. The quantity of streptomycin that EPA would allow to be sprayed on citrus is orders of magnitude greater than streptomycin's current use in human medicine. Streptogramins are considered highly important for human medicine by the United States Food and Drug

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Administration (FDA)[8] Streptomycin is classified by FDA as highly important in human medicine and is used to address hard-to-treat tuberculosis infections, and bubonic plague, among other diseases. EPA's evaluation of the risk of increased antibiotic resistance is seriously flawed.

EPA has also failed to adequately consider risks to non-target species, particularly honey bees. EPA did not evaluate streptomycin's potential effect on the bees' gut microbiome, which could make them more susceptible to disease.

We urge EPA not to allow the use of this medically important antibiotic in citrus production to combat plant diseases. If use is permitted, EPA should restrict application to injection of infected trees, rather than canopy spraying. At a minimum, we urge EPA to classify it as a Restricted Use Pesticide, so that it can only be applied by licensed trained applicators.

We recognize the hardship that the spread of this disease is creating for citrus growers, but we argue that the industry wide routine use of antibiotics that is anticipated by this registration request runs counter to the most basic principles of antimicrobial stewardship.

Bacterial outbreaks that are linked to citrus juice also represent a direct public health threat and increasing antibiotic resistance only adds to that threat. An important tool for combating the spread of antibiotic resistance is recognizing the need to consider human, animal, and environmental health together. All uses of antimicrobials and exposures must be considered as contributing to the crisis of resistance and that any increase in use should be considered suspect.

Before allowing the huge proposed increase of the use of this highly important antimicrobial under conditions very likely to select for resistance and for purposes that do not mitigate either animal or human suffering, the EPA must assess more fully the potential impacts on the health of the environment, workers, and consumers.

<u>EPA must consider risk to animal and plant health resulting from disruption of microbial ecosystems</u>

EPA's Assessment of Ecological Risk[9] completely ignores the unique potential for antimicrobials to disrupt microbial ecosystems[10] and the impacts of that disruption on the ecosystem as a whole. Bacteria provide essential ecosystem functions[11], but the PRD does not even consider impacts of the use of streptomycin on microbial communities. The only bacteria included in the Assessment of Ecological Risk are cyanobacteria and the assessment finds that they are highly susceptible to streptomycin with a risk quotient of 2.5 with a level of concern 1.0 meaning "effects greater than 50% for sensitive species." Cyanobacteria provide crucial ecological services yet the PRD treats these key species in isolation from their role in the environment. The PRD ignores other bacterial populations that this approval will likely affect.

There is a growing body of research showing that the health of animals is highly dependent on the health of the microbial communities in and around them. The

disruption of human and animal associated microbiomes by antibiotics can have serious negative consequences. Given the EPA anticipates that streptomycin will be sprayed on almost 1200 square miles of land, it is imperative to first understand how the use of this potent antibacterial may affect bacterial communities including the microbiomes of the animals and people in the impacted area. EPA should not approve these new uses until it has assessed these risks.

EPA Cannot Authorize any Additional Uses of Streptomycin as Pesticide before First Complying with its Duties under the Endangered Species Act and FIFRA

In addition, the EPA must insure that any approved uses of streptomycin as a pesticide do not jeopardize species protected under the Endangered Species Act (16 U.S.C. § 1536) or adversely modify or destroy their critical habitat including disrupting the microbiological ecosystems that support their health. As a discretionary action that may affect endangered and threatened species, EPA cannot approve this proposed new use without first completing consultation under the ESA with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service. Without such consultation, EPA cannot satisfy its duties under the ESA. Moreover, unless and until the EPA completes ESA consultation, any taking of protected species from the use of this pesticide is unlawful.

Effect on Honey Bees

Of particular concern is the impact of streptomycin on pollinators, such as the honey bee, which is attracted to citrus flowers. EPA states that streptomycin is classified as "practically nontoxic" to honey bees on an acute exposure basis.[12] However, EPA's risk assessment did not consider studies showing that antimicrobials can have an adverse effect on the honey bee microbiome, which could increase its susceptibility to disease. A 2017 study found that streptomycin and penicillin disrupted the gut bacteria (microbiome) of honey bees, decreasing the immune response and making the honey bee more vulnerable to infection by the microsporidian parasite Nosema ceranae, which is already a huge problem for honey bees.[13] Since the first application of streptomycin would be during the flowering period, honey bees that are visiting citrus flowers for nectar could be exposed to significant amounts of streptomycin.

There is also a possibility that honey bees could disperse streptomycin resistance genes (strA-strB), something EPA should evaluate before allowing this use of streptomycin. A study published in 2018[14] found that the strA-strB genes from the Tn5393 transposon can be detected in the gut microbiota of honey bees, noting that the study is "the first to report horizontal gene transferred (HGT) streptomycin resistance genes (strA-strB) in a honeybee gut symbiont. Our data suggest a direct link between the use of streptomycin in crop farming and dispersal of streptomycin-resistant genes." The same study also noted that an identical Tn5393 had previously been identified in E. coli plasmid pVI-W9608, so clearly the Tn5383 transposon can transfer between distantly related bacteria, including plant pathogens and human pathogens. Although the Tn5393 transposon has not been found in CLas or the Xanthomonas citri citri, the target organisms, it has been found in related Xanthomona species, suggesting that it may be

able to move into Xcc. The reason Tn5393 has not been found in CLas is likely due to the fact that CLas is an unculturable bacteria, so it can't be grown and studied in the lab.

Honey bees are major pollinators in US agriculture and are often shipped long distances to pollinate crops. The fact that the Tn5393 transposon can move into gut bacteria of honey bees means that there is now the potential for widespread movement of the strA-strB genes within the honey gut microbiome and between habitats due to shipment of honey bees for pollination purposes. EPA has not addressed this risk. EPA should not go forward with this decision without requiring significantly more data on effects on pollinators, especially the impact on microbiome, disease susceptibility, and potential for resistance gene transfer and spread to far flung environments as the honey bees are moved throughout the country to pollinate different crops.

<u>EPA should consider evidence when assessing the antimicrobial resistance risk and risk mitigation measures for workers</u>

EPA acknowledges the potential risks of antibiotic resistance resulting from workers handling streptomycin or working in fields where it has been used[15]. In order to mitigate this risk, EPA proposes requiring protective clothing without providing any evidence that the proposed measures will actually work. Before approval, EPA should require studies of workers handling the pesticide under field conditions to determine whether the exposures under prosed conditions of use lead to the development of resistance and to determine whether the exposure affects the workers microbiome both skin and gut.

As for the protection of workers spraying the antibiotic, EPA requires that workers wear gloves, clothes, protective eyewear, a respirator and a neck covering. Since this is not a restricted use pesticide, non-professional applicators can apply it and there is a greater potential for misuse, particularly under hot and humid conditions, than if only professional applicators could use it. We urge EPA, if it is to approve canopy spraying, to classify streptomycin as a Restricted Use Pesticide.

While EPA so far appears to have given only very limited consideration to the concerns of CDC and FDA regarding judicious use, drift mitigation or protection for workers using the product, EPA has proposed a time-limited registration of 7 years. EPA says this will give it an opportunity to gather data on antimicrobial resistance trends, and near the end of that registration to go back to CDC and FDA to see if they still have concerns: "a time-limited registration of 7 years on the citrus will allow for a more complete picture of evolving microbial resistance trends … EPA's consultation with our federal partners prior to the end of the time-limitation period will allow the Agency to incorporate any new medical/veterinary use information and concerns on streptomycin use into a new current risk picture for streptomycin." While a 7-year review may prove useful, given the urgency of the antibiotic resistance problem, and the need to prevent resistance rather than waiting for it to develop before taking action, we urge EPA to give those agencies' concerns proper consideration now.

EPA should improve antimicrobial resistance risk assessment and apply risk mitigation measures commensurate with the risk

The PRD considers impacts on consumer from the development of antibiotic resistance using a framework for assessing the risk based on a guidance (GFI#152) developed by the FDA to evaluate the safety of antimicrobial new animal drugs. [16] We have serious concerns about how EPA carried out the assessment of antimicrobial resistance risk. First, under GFI#152, the initial step in an assessment is a hazard characterization, which identifies the bacterial pathogens the proposed use will likely impact. The failure to include this step in the streptomycin safety assessment has led to the assessment at times confusing concerns about resistance in the target organism with concerns about resistance to bacteria of human health concern. The EPA should redo the assessment with clearer information on what are the hazards of concern. Second, EPA has modified the release assessment from "high" in the review of the submitter's safety assessment[17] to medium in the PRD[18] without explanation or acknowledgement. This should be reverted to high unless EPA provides evidence supporting the change. Given the medium exposure and the "highly important" ranking of the aminoglycoside class, the overall ranking is medium risk that antimicrobial resistance from the proposed use will harm human health.

FDA (GFI#152, page 25) recommends the following restrictions for drugs considered a medium risk: 1) require veterinary oversight, 2) limit extent of use to low or medium and 3) post-approval monitoring of resistance in animals and food. The risk mitigation measures in the PRD for this medium risk use fall far short of these recommendations and far short of what is needed to protect human health. Oversight from a veterinarian is not relevant in plant agriculture, but there is precedence for having a professional involved in the use of an antibiotic with this risk profile. Making streptomycin a restricted use pesticide (RUP) would ensure that people who were not professionals did not use this product. Under GFI#152 (page 23) any herd or flock-wide use of a drug is considered high extent of use. EPA is proposing that this drug potentially be used on every acre of citrus year after year. This is in no way the limited extent of use that is consistent with a medium risk antimicrobial use. If EPA were to restrict use to a limited set of high-risk areas consistent with GFI#152, then EPA must still require other risk mitigation steps. Consistent with GFI#152, EPA should require sampling of both growing areas and crops for development of resistance. The proposed risk mitigation steps fall far short of what is needed based on the sponsor and EPA's assessment of risk

Conclusion

Center for Food Safety asks that EPA not approve streptomycin for management of HLB and Xanthomonus citri subsp. Citri (Xcc) until it has adequately addressed the risk to the environment (particularly pollinators like the honeybee), workers, and consumers from this potentially massive expansion of the use of this highly important antibiotic.

Any approval for streptomycin use should require a lot more data. If use is approved, any use should only be via trunk injection. EPA should classify streptomycin as a Restricted Use Pesticide so it can only be applied by a licensed trained applicator.

Sincerely,

Jaydee R. Hanson
Policy Director

[1] www.regulations.gov Document ID: EPA-HQ- OPP-2016-0067-0023
[2] PRD, p. 11
[3] PRD, p. 14
[4] PRD, p.14
[5] EPA-HQ-OPP- 2016-0067-0015, page 7
[6] FDA, 2012 https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435.pdf
[7] FDA, 2017 https://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM628538.pdf
[8] FDA, Appendix A of Guidance for Industry #152 available at:
https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf
[9] PRD pages 3-5.
[10] Grenni P, Ancona V,Barra Caracciolo A Ecological effects of antibiotics on natural ecosystems: A review Microchemical Journal (2018) 136 25-39 https://www.sciencedirect.com/science/article/pii/S0026265X17301108
[11] Falkowski PG1, Fenchel T, Delong EF. The microbial engines that drive Earth's biogeochemical cycles. Science. 2008 May 23;320(5879):1034-9. http://science.sciencemag.org/content/320/5879/1034.long
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[12] PRD, Pg. 4
[13] Li JH, Evans JD, Li WF, Zhao YZ, DeGrandi-Hoffman G et al. 2017. New evidence showing that the destruction of gut bacteria by antibiotic treatment could increase the honey bee's vulnerability to Nosema infection. PLOS ONE doi.org/10.1371. At: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0187505&type=printable
[14] Ludvigsen J, Amdam GV, Rudi K and TM L'Abee-Lund. 2018. Detection and characterization of streptomycin resistance (strA-strB) in a honeybee gut symbiont (Snodgrassella alvi) and the associated risk of antibiotic resistance transfer. Microbial Ecology doi/10.1007/s00248-018-1171-7
[15] PRD, p.12
[16] PRD, pages 10-13.
[17] EPA-HQ-OPP-2016-0067-0023, page 6
[18] PRD, p.11