

January 19, 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)

Keep Antibiotics Working (KAW) 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 *Xanthomonas citri* subsp. *Citri* (Xcc), the causal agent of citrus canker disease. As is clearly indicated in the Proposed Registration Decision ([EPA-HQ-OPP-2016-0067-0023](#)), approving the new uses would result in a massive increase in agricultural use of this highly important drug. In the Proposed Registration Decision hereafter “PRD” 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 (PRD, page 11). This in itself is a stunning admission for the use of a medically important antibiotic. The anticipation is that every member of the target population is going to receive the same antibiotic multiple times every year into the foreseeable future. At the same time, the EPA and the drug registrants recognize that the antibiotic will only suppress not treat the disease (PRD, page 14) and it will be impossible to test for the development of resistance in the target pathogen because it is not culturable (PRD, page 11). This is totally contrary to all standards of antimicrobial stewardship.

EPA anticipates that citrus growers will use 1.02 pounds of streptomycin annually per acre (PRD, page 2). Applied to the total U.S. citrus crop of 764,000 acres, this use results in 77928 pounds or 353475 kg per year of active ingredient. EPA reports that 36000 pounds of streptomycin are used annually on crops other than citrus ([EPA-HQ-OPP-2016-0067-0015](#), page 7), so this approval could result in 22 times more streptomycin use in citrus than on all other crops. This amount is 54 times the total amount of the 6485 kg of aminoglycosides used in human medicine ([FDA, 2012](#)) and 1.4 times the 259184 kg sold for use in animals in 2017 ([FDA, 2018](#)).

While we recognize the hardship that the spread of this disease is creating for citrus producer, we believe 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.

Antibiotic resistance is a major global public health crisis that threatens to reverse much of the medical progress made in the 20th century and return us to a time when a scratch or throat infection routinely killed. The United States Centers for Disease Control and Prevention (CDC) [reports](#) that there are currently over two million illnesses and over 23,000 deaths from resistant infections in the U.S. each year and these numbers are [almost certain to rise](#) unless we do much more to combat the spread of resistance. The use of antimicrobials—whether in human medicine, animal agriculture, or in crop production—is a major factor in the spread of resistance, and increasing use will likely contribute to increased resistance. Streptogramins are considered highly important for human medicine by the United States Food and Drug Administration (FDA) ([Appendix A of Guidance for Industry #152](#)).

Allowing such a massive expansion of the pesticide use of antibiotics, over twenty two times the current use for this class of highly important drugs, at a time when resistance to antibiotics is a leading public health crisis would be the height of folly. [Bacterial outbreaks linked to citrus juices](#) represent a direct public health threat and antibiotic resistance only adds to that threat. An important tool for combating the spread of antibiotic resistance is the [One Health](#) framework that recognizes the need to consider human, animal, and environmental health together. Taken seriously, this framework indicates that all uses of antimicrobials 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.

EPA must consider risk to animal and plant health resulting from disruption of microbial ecosystems

EPA's Assessment of Ecological Risk (PRD pages 3-5) completely ignores the unique potential for antimicrobials to disrupt microbial ecosystems ([Grenni, 2018](#)) and the impacts of that disruption on the ecosystem as a whole. Bacteria provide essential ecosystem functions ([Falkowski, 2008](#); [van der Heijden, 2008](#)), 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 ([Diez, 2013](#)) 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 ([Kim, 2017](#); [Becattini, 2017](#)). Negative impacts on health from disruption of microbiomes by antimicrobials have been shown for mammals ([Schokker, 2015](#); [Looft, 2012](#)), birds ([Clavijo, 2018](#)), amphibians ([Holden, 2015](#)), and terrestrial invertebrates ([Raymann, 2017](#)). 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.

EPA should consider evidence when assessing the antimicrobial resistance risk and risk mitigation measures for workers

EPA acknowledges the potential risks of antibiotic resistance resulting from workers handling streptomycin or working in fields where it has been used (PRD 12). 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 proposed conditions of use lead to the development of resistance and to determine whether the exposure affects the workers microbiome both skin and gut.

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 (PRD, pages 10-13). KAW has 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 ([EPA-HQ-OPP-2016-0067-0023](#), page 6) to medium in the PRD (page 11) 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 flockwide 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

KAW asks that EPA not approve streptomycin for management of HLB and *Xanthomonas citri* subsp. *Citri* (Xcc) until it has adequately addressed the risk to the environment, workers, and consumers from this potentially massive expansion of the use of this highly important antibiotic.

Sincerely,

Steven Roach
Keep Antibiotics Working
www.keepantibioticsworking.org