**Comments of Consumer Reports**
**on**
**EPA's Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10**
**Docket No. EPA-HQ-OPP-2016-0067; EPA Reg. No. 71185-4, 80990-3, 80990-4**

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Consumer Reports welcomes the opportunity to comment on the Environmental Protection Agency's (EPA) proposal to allow new uses of the active ingredient streptomycin sulfate on citrus crop group 10-10 to control the bacterium *Candidatus* Liberibacter asiaticus (CLas), the causal agent of citrus huanglongbing (HLB), also known as citrus greening disease, and the bacterium *Xanthomonas citri citri* (Xcc), the causal agent of citrus canker disease.

Consumer Reports is an independent U.S. non-profit organization that works side by side with consumers for truth, transparency and fairness in the marketplace, through research, testing, journalism and advocacy.[1] We have more than 6 million members, and more than 1.7 million volunteers and online activists. Consumer Reports seeks to establish strong pro-consumer policies and protections to create a fairer, safer and healthier world.

EPA proposes to allow streptomycin to be sprayed on all citrus trees in the United States, up to three times a year. Based on current commercial citrus acreage, the amount allowed to be sprayed totals more than 900,000 lb. We urge EPA to reverse its decision to allow use of streptomycin in citrus, which would represent a 26-fold increase in the amount of streptomycin used in plant agriculture, since such use could pose unacceptable risks to human health and the environment, risks which have not been adequately investigated. 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. 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. The quantity of streptomycin that EPA proposes to allow to be sprayed on citrus is more than 66 times the amount of aminoglycosides (which includes streptomycin) used in human medicine. This large increase in use increases the chance of development of

[1] www.consumerreports.org

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resistance due to the increased selection pressure. 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.

**Background**

Antimicrobial resistance is a growing global problem that threatens human health in the United States and throughout the world.[2] The Centers for Disease Control and Prevention (CDC), estimates that in the United States, each year, at least 2 million people acquire serious infections with bacteria that are resistant to one or more antibiotics and at least 23,000 people die as a result.[3] The Infectious Disease Society of America (IDSA) notes that the annual cost of infections caused by antibiotic-resistant pathogens is between $21 and $34 billion and that "Antimicrobial resistance is recognized as one of the greatest threats to human health."[4]

Experts agree that antibiotic use in human medicine and plant and animal agriculture should be reduced in order to slow development of resistance.[5] FDA, in an effort to reduce antibiotic use in animal agriculture, issued regulations and guidance that ended all use of medically important antibiotics for growth promotion and required a veterinarian's supervision for use in disease prevention and treatment, in 2017.[6] Streptomycin, an aminoglycoside antibiotic, is classified by the US Food and Drug

[2] O'Neill J (Chair). 2016. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations The Review on Antimicrobial Resistance*. At: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
[3] U.S. Centers for Disease Control (CDC). 2013. Antibiotic Resistance Threats in the United States, 2013. At: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
[4] IDSA. 2016. Antimicrobial Resistance: A Public Health Crisis. At: https://www.idsociety.org/globalassets/idsa/topics-of-interest/antimicrobial-resistance/idsa-antibiotic-resistance-infographic-2016-final.pdf
[5] O'Neill J (Chair). 2016. *Op cit.*
[6] https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm628504.htm

Administration (FDA) as highly important in human medicine.[7] It is used to treat, among other things, tuberculosis when other antibiotics have failed; bubonic plague; tularemia; brucellosis; *E.coli, Proteus, A. aerogenes, K. pneumoniae, and Enterococcus faecalis* in urinary tract infections; *K. pneumoniae* pneumonia (concomitantly with another antibacterial agent); and *Streptococcus* viridans, *Enterococcus faecalis* (in endocardial infections -concomitantly with penicillin).[8]

EPA is authorizing a massive increase in the use of this antibiotic dwarfing use in human medicine, and exceeding current use in any other agricultural sector. The EPA notes that, "[t]he rapidly spreading and devastating nature of HLB makes it plausible that the full label-rate will be used on all affected citrus acreage."[9] The requested uses are for up to three ground spray applications of 0.45 lb of streptomycin sulfate per acre, for a maximum annual rate of 1.35 lb streptomycin sulfate per acre. Since according to USDA's National Agricultural Statistics Service, there was 697,900 acres of citrus planted in 2017[10], this would mean that 940,000 lb, or 428,000 kg, would be used on citrus per year. By comparison, currently, some 36,000 lb of streptomycin sulfate are used to control disease in apples and pears.[11] Thus, the proposed usage of streptomycin sulfate in citrus would represent over a 26-fold increase in streptomycin use in plant agriculture.

The 428,000 kg of streptomycin would also be 1.6 times the 259,184 kg of aminoglycosides (which include streptomycin) sold for use in animals in 2017.[12] The proposed citrus use is more than 66 times the 6,485 kg of aminoglycosides used in human medicine in 2011.[13]

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[7] FDA. 2003. 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: https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf

[8] https://www.drugs.com/pro/streptomycin.html

[9] Pg. 11 in EPA 2018. Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10. 2018. At: https://www.regulations.gov/searchResults?rpp=25&po=0&s=epa-hq-opp-2016-0067-0023&fp=true&ns=true

[10] USDA. 2018. Citrus Fruits 2018 Summary. At: https://www.nass.usda.gov/Publications/Todays_Reports/reports/cfrt0818.pdf

[11] EPA. Collins S and JL Kough. 2017. Review of AgroSource's analysis of streptomycin's safety with regard to its microbiological effect on bacteria or human health concern (FDA/CVM Guidance to Industry #152) for a Section 3 registration on citrus crop group. October 25, 2017. At: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0067-0015

[12] FDA. 2018. 2017 Summary Report on Antimicrobials sold or Distributed for Use in Food-Producing Animals. At: https://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM628538.pdf

[13] Pham T. 2012. FDA Drug Use Review, Apri 5, 2012. At: http://webcache.googleusercontent.com/search?q=cache:https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435

This massive increase in use of streptomycin in plant agriculture runs counter to the strenuous efforts currently being made to reduce antibiotic use in animal agriculture and human medicine, both nationally and globally.[14] It is not an appropriate action considering the public health crisis that antibiotic resistance poses.

**Assessment of Ecological Risks**

EPA's environmental risk assessment is inadequate. Its Assessment of Ecological Risk fails to adequately consider the potential for antimicrobials to disrupt microbial ecosystems in the soil, on the plant, and in non-target organisms. In addition, it also fails to consider the potential impact of streptomycin on the microbiomes of humans, animals and insects. We are particularly concerned about the inadequacy of EPA's consideration of effects on honey bees.

*Effect on Honey Bees*

Of particular concern is the impact of streptomycin on pollinators, such as honey bees, which are attracted to citrus flowers. EPA states that streptomycin is classified as "practically nontoxic" to honey bees on an acute exposure basis.[15] 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.[16] 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 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

[14] https://www.who.int/antimicrobial-resistance/global-action-plan/en/
[15] Pg. 4 in EPA. 2018. *Op cit.*
[16] 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

streptomycin in crop farming and dispersal of streptomycin-resistant genes."[17] 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 *Xanthomonas* 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.

*Effect on Microbiomes of Other Species*

EPA proposed decision cites data showing that streptomycin is "practically nontoxic" to birds[18] and mammals.[19] However, EPA does not consider whether antibiotics are likely to have an impact on microbiomes of these species. There is a good deal of work showing that disruption of microbiomes in mammals,[20] birds,[21]

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[17] 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

[18] Pg. 4 in EPA. 2018. *Op cit.*

[19] Pg. 5 in *Id.*

[20] Becattini S, Taur Y and EG Palmer. 2016. Antibiotic-induced changes in the intestinal microbiota and disease. *Trends in Molecular Medicine* 22(6): 458-478. At: https://www.cell.com/action/showPdf?pii=S1471-4914%2816%2930007-7 ; Schokker D, Zhang J, Vastenhouw SA, Hellig HGHJ, Smidt H, Rebel JMJ and MA Smits. 2015. Long-lasting effects of early-life antibiotic treatment and routine animal handling on gut microbiota composition and immune system in pigs. *PLOS One*, DOI:10.1371. At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4319779/pdf/pone.0116523.pdf

[21] Borda-Molina D, Seifert J and A Camarinha-Silva. 2015. Current perspectives of the chicken gastrointestinal tract and its microbiome. *Computational and Structural Biotechnology Journal* 16: 131-139. At: https://www.sciencedirect.com/science/article/pii/S2001037017301162

amphibians[22] and terrestrial invertebrates[23] can have negative health impacts on those organisms, and that antibiotics can cause disruption of microbiomes. Organisms that are living in the citrus orchard ecosystem could encounter residues of streptomycin in the water they drink, consumption of citrus fruits or leaves, or be exposed to the canopy sprays, or if they are eating other organisms that have contacted the spray. EPA has not assessed how a number of species that are likely to be exposed to streptomycin sprays will be affected and in particular how their microbiome might be affected. This should be done before use is allowed.

*Human Safety*

Humans may be exposed to low levels of streptomycin either through consumption of citrus juice or via drinking water if they live in citrus producing areas. EPA has proposed tolerances for streptomycin residues of 2 ppm for citrus fruits and 6 ppm for dried fruit pulp.[24] Since streptomycin does not concentrate during processing that means that there could be up to 2 ppm of streptomycin in juice. In addition, as part of their risk assessment, EPA calculated that in the worse case, e.g., use of streptomycin on all acreage of citrus and maximum allowed rates, the result in drinking water would be "acute exposure [of streptomycin] of 932 parts per billion (ppb), and for chronic exposures (non-cancer) is estimated at 760 ppb.[25]

These low residue and drinking water levels can pose a real risk. A 2011 study by Swedish scientists showed that an extremely low level of streptomycin, 1 ppm, dubbed the "minimal selective concentration," was enough to not only select for pre-existing resistance in *Salmonella typhimurium*, but also new mutants: "The data … show that these sub-MIC [minimum inhibitory concentration] levels of antibiotic do not only enrich for pre-existing resistant mutants, but they can also select for resistant mutants *de novo* from a susceptible population."[26] In addition, the problem of "minimal selective concentration" is such that a 2016 Swedish study has proposed using MSCs to develop "presumed no-effect concentrations" for various antibiotics to be used to set regulatory

[22] Kueneman JG, Parfrey LW, Woodhams DC, Archer HM, Knight R and VJ McKenzie. 2013. The amphibian skin-associated microbiome across species, space and life history stages. *Molecular Ecology* doi:10.1111. At: https://s3.amazonaws.com/academia.edu.documents/45437884/The_amphibian_skin-associated_microbiome20160507-27702-15co9tu.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=1552095763&Signature=%2FH54YQeyWh6J%2F9vk7mmVxRYStCI%3D&response-content-disposition=inline%3B%20filename%3DThe_amphibian_skin-associated_microbiome.pdf

[23] Raymann K, Shaffer Z and NA Moran. 2017. Antibiotic exposure perburbs the gut microbiota and elevates mortality in honeybees. *PLOS Biology* DOI:10.1371. At: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.2001861

[24] https://www.govinfo.gov/content/pkg/FR-2017-03-15/pdf/2017-04779.pdf

[25] Pg. 13761 in *Id.*

[26] Pg. 5 in Gullberg E, Cao S, Berg OG, Illback C, Sandegren L, Hughes D and DL Andersson. 2011. Selection of resistant bacteria at very low antibiotic concentrations. *PLOS Pathogens* 7(7):e1002158. At: https://journals.plos.org/plospathogens/article/file?id=10.1371/journal.ppat.1002158&type=printable

limits for antibiotics.[27] The fact that the permitted residue level of streptomycin in juice is double this minimum selective level suggests a clear risk of exacerbating streptomycin resistance. We urge EPA to assess the risk of selection for antibiotic resistance in the human gut resulting from levels of streptomycin in fruit juice or in drinking water in citrus growing areas and to consider setting a tolerance level that will be below the minimum selective concentration before allowing streptomycin use in citrus.

**Antimicrobial Resistance Assessment**

EPA attempted an antimicrobial resistance assessment, using as a model FDA's Guidance for Industry (GFI) 152 on Evaluating the Safety of Antimicrobial Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern. According to GFI 152, the assessment should start with a hazard characterization, followed by a qualitative antimicrobial resistance risk assessment that includes a release assessment, exposure assessment, consequence assessment and then risk estimation.[28] Finally, there should be an antimicrobial risk management strategy. There are deficiencies in how EPA carried out the framework at every stage as well as in their antimicrobial risk management strategy. Nevertheless, the analysis, by an EPA biologist and microbiologist, recommended that "use of streptomycin in citrus should be contingent on establishing baseline data on streptomycin resistance and the presence of bacteria of human health concern in citrus orchards. A monitoring plan for the presence of streptomycin resistant..bacteria...should be implemented with reports made to the Agency."[29] However, EPA has not fully adopted even these limited Recommendations in its proposed registration decision.

At the start, EPA failed to do a hazard characterization, which GFI 152 says should be separate from the qualitative risk assessment and submitted as a stand-alone document. The hazard characterization should include the bacterial species and strains for which resistance acquisition has potential human health consequences as well as the known resistance determinants and include genotypic similarities with resistance determinants in other food-borne bacteria. Since EPA did not do this hazard characterization, the discussion is jumbled, some times referring to resistance in the plant

[27] Bengtsson-Palme J and DGJ Larsson. 2016. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International* 86: 140-149. At: https://www.sciencedirect.com/science/article/pii/S0160412015300817#bb0180

[28] FDA. 2003. 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: https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf

[29] Pg. 3 in EPA Collins S and JL Kough. 2017. 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. October 25, 2017. At: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0067-0015

pathogen and other times referring to some human pathogens. EPA should do a hazard characterization to make clear which hazards are of concern.

In terms of the qualitative risk assessment, EPA has assigned a release assessment rating of "medium" when a rating of "high" appears justified. In the EPA staff review of the applicant company's (AgroSource, Inc) analysis based on GFI 152, an EPA microbiologist noted that the "release assessment rating for the proposed uses of streptomycin would be expected to be 'high' for the proposed citrus use."[30] This makes sense since the proposal is to spray every acre of citrus in the US three times a year. This clearly is a "high" release scenario. Yet, in the Proposed Registration Document, the release assessment rating has been listed as "medium" "based on the information available for streptomycin control of Xcc."[31] However, they go on to note that HLB is such a severe disease that it "makes it plausible that the full label-rate will be used on all affected citrus acreage."[32] Clearly, use of streptomycin on every acre of citrus in the U.S. constitutes a "high" release assessment. EPA should base the release assessment on HLB, not the data it might have on Xcc, and change the release assessment to "high."

For the exposure assessment, EPA estimates that exposure from consuming treated foods yields a rating of "medium." In terms of the consequence assessment, EPA has determined that it is "highly important" since streptomycin is considered "highly important" in human medicine. EPA does note that the assessment may change to "critical" if it has been shown that use in citrus affects the clinical efficacy of streptomycin or selects for multiple drug resistance.

With a release assessment of "medium," an exposure assessment of "medium" and consequence assessment of "highly important," the overall risk estimate in a GFI 152 antibiotic resistance risk assessment becomes "medium." GFI 152 states that an overall risk estimate can be used to help identify the steps to manage the risk associated with the proposed new antimicrobial drug usage. Table 8 in GFI 152 lays out appropriate risk management steps based on the level of risk. For a "medium" risk, FDA recommends the following risk management steps: 1) drug should only be available by a prescription or veterinary feed directive, 2) limit extent of use to low or medium, 3) require post-approval monitoring.

The proposed risk management steps in the EPA Proposed Registration Document do not meet the standard suggested by FDA. First, requiring a veterinarian's prescription is not appropriate for plants, but EPA could require professional use. If EPA rated the product as a Restricted Use Pesticide, only a licensed professional (trained) pest control

[30] Pg. 6 in *Id.*
[31] EPA. 2018. Proposed Registration Document for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10. At: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0067-0023
[32] Pg. 11 in *Id.*

operator could apply the pesticide. But, EPA decided not to make it a Restricted Use Pesticide; they simply decided that the label would say that it "should" be used by a professional. Based on its GFI # 152 analysis we urge EPA to classify streptomycin, if approved for use in citrus, as a Restricted Use Pesticide.

Second, in terms of extent of use, treating every acre of citrus in the U.S. would appear to constitute a "high" extent of use since, according to Table 7 in the GFI 152 which states, "administration to flocks or herds of animals is defined as administration to all animals within a building, house, feedlot." Clearly, by analogy, treating all citrus trees in a single farm, much less all citrus trees in the U.S. would appear to be a "high" extent of use. This classification has important implications for EPA's decision. According to Table 8, in the FDA risk management scheme, high extent of use should only be allowed for "low" risk antimicrobials, which streptomycin is not. Even if EPA were to try to restrict this drug to "medium" extent of use, that would still mean (analogizing from a flock) that only a subset of trees in an orchard could be treated, which is not what is being proposed.

Three, in terms of post-approval monitoring, EPA also fall short of what the FDA recommends in its risk assessment model. EPA says it will require monitoring with "Required protocol submissions on a yearly basis for the first 3 years describing how the registrant plans to monitor soils and citrus for incidences of antibiotic resistance."[33] However, EPA does not give any suggestions for which bacteria and antibiotic resistance elements should be looked for. Also, as EPA notes, "Since the HLB bacterium cannot be cultured with existing methods, there is no information on selection for streptomycin resistance."[34] How can the registrant monitor for resistance in CLas if they cannot even culture it? If they cannot monitor for the resistance, how can this even be a judicious use of an antimicrobial, especially one that is highly important for human medicine? We urge EPA, if this use is approved, to require a monitoring method which is practical and feasible to carry out.

*Transfer of Resistance*

EPA has additionally failed to adequately consider the problem of transfer of resistance to streptomycin. There are two main sources of streptomycin resistance genes—those that are on a chromosome and those that are on mobile elements (such as plasmid, transposon, and integrin). Although there are many streptomycin resistance genes, the main ones on mobile elements are the *strA-strB* genes that can more readily transfer between bacteria. The *strA-strB* genes are often found on the transposon Tn5393. The fact that *strA-strB* genes on Tn5393 are found in wide range of environmental and pathogenic bacteria "suggests that gene transfer events between

[33] Pg. 16 *Id.*
[34] Pg. 11 *Id.*

human, animal, and plant-associated bacteria have occurred."[35] The Tn5359 transposon has been found frequently, and was first noted in the bacteria *Erwinia amylovora* that causes fire blight disease in apples and pears.[36] A study in Italy that looked at 58 multidrug-resistant *Salmonella enterica* strains found that 84 percent of the streptomycin-resistant strains contained *strA-strB* genes.[37] In some 16 strains, the *strA-strB* genes also included part of the Tn5393 transposon, which had previously only been found in *Erwinia amylovora*. As the paper noted, "it may be hypothesized that *Salmonella* imported this genetic element from plant pathogens, probably through the contamination of animal feeds."[38]

It should also be pointed out that there have been a number of outbreaks of illness associated with orange juice, including a 2005 outbreak of *Salmonella* Typhimurium and Saintpaul in unpasteurized orange juice that sickened 152 people in 23 states.[39] Since *strA-strB* in TN5393 can move from plant bacteria into *Salmonella*, there clearly could be an increased human health risk. The question is whether *strA-strB* in TN5393 can be found in either CLas or Xcc and, if so, can it move from citrus to pathogens of human concern. Although *strA-strB* in TN5393 has been found in neither CLas nor Xcc, the fact that CLas is unculturable would make it very difficult to study resistance in that bacterium. Other species of *Xanthomonas* related to citrus canker, such as *Xanthomonas campestris*, have been found to harbor *strA-strB* in TN5393.[40]

This problem is not adequately addressed in any of the EPA documents supporting its registration decision. We urge EPA to explicitly require monitoring, especially of *strA-strB* in TN5393, in Xcc, and other bacteria in the environment. We note that EPA will require the company to monitor for resistance, but it does not give any details for which particular resistance gene(s) and which bacterial species should be included, so we cannot tell how thorough this monitoring will be.

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[35] Pg. 133 in Sundin GW and CL Bender. 1996. Dissemination of the *strA-strB* streptomycin-resistance genes among commensal and pathogenic bacteria from humans, animals, and plants. *Molecular Ecology* 5: 133-143. At: https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1365-294X.1996.tb00299.x

[36] Chiou CS and AL Jones. 1993. Nucleotide sequence analysis of a transposon (Tn5393) carrying streptomycin resistance genes in *Erwinia amylovora* and other gram-negative bacteria. *Journal of Bacteriology* 175(3): https://jb.asm.org/content/jb/175/3/732.full.pdf

[37] Pezzella C, Ricci A, DiGiannatale E, Luzzi I and A Carattoli. 2004. Tetracycline and streptomycin resistance genes, transposons, and plasmids in *Salmonella enterica* isolates from animals in Italy. *Antimicrobial Agents and Chemotherapy*, 48(3): 903-908. At: https://aac.asm.org/content/aac/48/3/903.full.pdf

[38] Pg.. 907 in *Id.*

[39] Vojdani JD, Beuchat LR and RV Tauxe. 2008. Juice-associated outbreaks of human illness in the United States, 1995 through 2005. *Journal of Food Protection* 71(2): 356-364. At: https://jfoodprotection.org/doi/pdf/10.4315/0362-028X-71.2.356

[40] Sundin and Bender 1996. *Op cit.*

**Concerns of FDA and CDC**

EPA notes that there was concern from its federal partners, FDA and CDC, stating, "Our federal partners expressed a number of concerns on expanding uses of antibiotics in plant agriculture. *Overall, they recommend judicious use, prevention of drift to neighboring fields/water bodies, and additional protection of agricultural pesticide handlers from exposure*. Limiting unnecessary environmental and human exposure can reduce the potential for development of antibiotic resistance"[41] *italics* added. The restrictions that EPA proposes do not appear to adequately address the concerns of FDA and CDC.

*Judicious Use*

First, spraying of all citrus in the US does not constitute judicious use, which should involve minimizing use and addressing disease problems without antibiotics wherever possible. Although the label states "[u]se only to treat/prevent proven bacterial infections," the agency admits that streptomycin does not prevent or cure disease, it only slows progression: "While streptomycin treatments may inhibit HLB and canker development, pathogens are not killed by the treatment and long-term disease management will be necessary."[42] EPA recognizes that the long-term use of streptomycin to just manage the disease will clearly help select for resistance. EPA in fact suggests another set of steps that can be taken to minimize the chance of resistance. EPA suggests using streptomycin as part of an integrated disease management (IDM) program, which involves scouting, crop rotation, development of disease thresholds, as well as considering cultural and biological controls. IDM is clearly a superior approach to just spraying streptomycin. However, it is not required. EPA also suggests that streptomycin should be regularly rotated with other chemicals such as tetracycline to delay the evolution of resistance. However, studies from the medical literature show that cycling of antibiotics of different classes in intensive care units does not seem to work as expected, showing only limited efficacy for preventing bacterial resistance.[43] We urge EPA to require that other methods of fighting this disease be employed as first choices.

[41] Pg. 17 in EPA PRD
[42] Pg 17 *Id*
[43] Kollef MH. 2006. Is antibiotic cycling the answer to preventing the emergence of bacterial resistance in the intensive care unit? *Clinical Infectious Disease*, 43(Supplement 2): S82-S88. At: https://academic.oup.com/cid/article/43/Supplement_2/S82/333644; van Duijin PJ, Verbrugghe W, Jorens PG, Spohr F, et al. 2018. The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: a cluster-randomized crossover trial. *The Lancet Infectious Diseases* 18(4): 401-409.

*Prevention of Drift*

To reduce environmental exposure, the label states, "To help reduce off-target drift, direct spray into the canopy, and turn off outward pointing nozzles at row ends and when spraying outer rows."[44] Although good advice, this hardly prevents drift into neighboring fields or waters. Spraying of streptomycin into the canopy of trees is bound to result in drift. The label puts no restriction on wind speed cut off, thus allowing the spraying to happen in very windy conditions. Another option that would drastically reduce the environmental exposure, which EPA fails to recommend, is trunk injection. A 2018 study showed that injection of streptomycin did lead to significant reduction of *C*Las in the trees and higher fruit yields, while a combination of streptomycin and oxytetracycline provided longer term control (6 to 8 months).[45] Yet EPA never mentions trunk injection. By injecting the antibiotic, it all goes into the tree, resulting in virtually no drift, less runoff and significantly lower exposure to non-target organisms including workers and neighbors, than with air blast canopy spraying. EPA should not approve streptomycin for canopy spraying. Any approval should only be for trunk injection.

*Worker Protection*

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 period 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."[46] While a 7-year review may prove useful, given the urgency of the antibiotic resistance problem, and the need to prevent

[44] Pg. 19 in EPA. 2018. *Op cit.*
[45] Hu J, Jiang J and N Wang. 2018. Control of citrus Huanglongbing via trunk injection of plant defense activators and antibiotics. *Phytopathology* 108: 186-195. At: https://apsjournals.apsnet.org/doi/pdf/10.1094/PHYTO-05-17-0175-R
[46] Pg. 16 in EPA. 2018. *Op cit.*

resistance rather than waiting for it to develop before taking action, we urge EPA to give those agencies' concerns proper consideration now.

**Conclusion**

The EPA's proposed decision would allow a massive expansion in plant agriculture, by 26-fold, in the use of streptomycin, a highly important medical antibiotic, in the U.S. Given the importance of reducing antimicrobial resistance, and given that EPA has not adequately addressed the risk to the environment (particularly pollinators like the honey bee), workers and consumers, we urge EPA not to approve streptomycin sulfate for management of *C*Las and Xcc at this time. Any approval for streptomycin use should require a lot more data. If use is approved, any use should only be via trunk injection. At a minimum EPA should classify streptomycin as a Restricted Use Pesticide so it can only be applied by a licensed trained applicator.