Consumer Reports Comments
On
EPA's Registration Review Proposed Interim Decisions for Several Pesticides:
Streptomycin
Docket No. EPA-HQ-OPP-20089-0687

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Consumer Reports welcomes the opportunity to comment on the Environmental Protection Agency's (EPA) Proposed Interim Registration Review Decision (PID) for the use of the active ingredient streptomycin in plant agriculture.

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.

Overview

The purpose of a PID is to re-evaluate a pesticide over time to ensure that it still can be safely used in plant agriculture, e.g., that as new scientific data emerges or new safety issues arise, the pesticide continues to meet the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Starting in 2006, EPA began a program to review each registered pesticide once every 15 years. FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, requires that the use of the pesticide will not cause unreasonable risks to human health or to the environment when used as directed on product labeling.

EPA's PID for streptomycin fails to show that currently approved uses meet this standard. This antibiotic has been approved for use as a pesticide against plant bacterial diseases in apples, pears and citrus and a number of vegetable crops for decades, but until recently, such uses were relatively modest, amounting to 55,300 pounds per year in total. In early 2019, however, EPA issued a Proposed Registration Decision for the new use of streptomycin sulfate on citrus crops which

[1] www.consumerreports.org

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would allow vastly increased spraying of this antibiotic--up to 900,000 pounds per year-- in citrus groves to combat citrus greening, raising new concerns about the development of antibiotic resistance.

This PID gives insufficient attention to, and does not adequately address, new concerns over the growing problem of antibiotic resistance, which scientific data shows results from overuse of antibiotics in both human medicine and agriculture, and which severely threatens human health. The PID acknowledges antibiotic resistance is a problem and includes new recommended labeling to reduce the risk such as "Animal grazing in treated areas is prohibited."[2] The new recommendations are positive steps. However, EPA's analysis of the risk, based primarily on current, very low usage in apples and pears, is inadequate and much stronger limitations are needed for potential use in oranges and grapefruit.

That continued use of streptomycin in apple and pear and, particularly, the large expansion in use in citrus in the entire U.S. could pose unacceptable risks to human health and the environment due to the spread of antibiotic resistance genes, risks which EPA has not adequately investigated. Consequently, this PID should have recommended a phase out of all uses of streptomycin in plant agriculture, including use in citrus. The risk of increased antimicrobial resistance is especially concerning, given more recent scientific understanding of how readily antibiotic resistance genes and elements can move between bacteria in the environment and in the gut of animals and other organisms.

EPA's recommendation in this PID to allow continued use of streptomycin in plant agriculture, including in citrus, stands in stark contrast to efforts by other parts of the US government to reduce antibiotic use in animal agriculture and human medicine. 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 has proposed to allow to be sprayed on citrus is more than 66 times the amount of aminoglycosides (which includes streptomycin) used in human medicine and us more than 25 times the amount presently used on apples and pears. This large increase in use increases the chance of development of 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, in this PID. EPA did not evaluate streptomycin's potential

[2] Pg. 24 in EPA 2018. Streptomycin Interim Registration Review Decision Case Number 0169. December 27, 2018. At: https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0687-0024

effect on the bees' gut microbiome, which could make them more susceptible to disease and also lead to the transmission of antimicrobial resistance genes to bacteria in the bees' gut microbiome, which could then be spread far and wide.

We urge EPA to revise this PID to end the use of this medically important antibiotic in plant production to combat plant diseases. If use is permitted in fruit trees, EPA should restrict application to injection of infected trees, rather than canopy spraying. At a minimum, we also urge EPA to classify streptomycin as a Restricted Use Pesticide, so that it can only be applied by licensed trained applicators.

Background and Context

Antimicrobial resistance is a growing global problem that threatens human health in the United States and throughout the world.[3] 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.[4] 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."[5]

Experts agree that antibiotic use in human medicine and plant and animal agriculture should be reduced in order to slow development of resistance.[6] 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.[7] Streptomycin, an aminoglycoside antibiotic, is classified by the US Food and Drug Administration (FDA) as highly important in human medicine.[8]

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[3] 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

[4] 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

[5] 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

[6] O'Neill J (Chair). 2016. *Op cit.*

[7] https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm628504.htm

[8] 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

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).[9]

EPA's PID for streptomycin concludes that, except for gauging the potential risks to threatened and endangered species, and the screening of streptomycin as a potential endocrine disruptor—both of which still remain to be done—that no new data are needed on potential human health and environmental impacts and that use of streptomycin can still be used safely in plant agriculture, as long a few changes are made to help mitigate the risk of adverse impacts due to antimicrobial resistance. The PID for streptomycin focuses primarily on uses of streptomycin to treat fire blight (caused by *Erwinia amylovora*) in apple and pear. Presently, annual use of streptomycin on apples and pears is 35,900 lbs.[10]

However, in 2016, EPA authorized use of streptomycin on oranges and other members of the citrus crop group 10-10 in Florida to combat citrus greening (caused by *Candidatus liberibacter Asiaticus*) and the bacterium *Xanthomonas citri citri* (Xcc), the causal agent of citrus canker disease. Since some 90% of citrus trees in Florida are attacked by citrus greening, EPA has decided to allow streptomycin to be sprayed on all citrus trees in Florida, up to three times a year. Then in early 2019, EPA proposed allowing streptomycin to be used on all citrus in the U.S. to treat for citrus greening, as well as citrus canker disease. EPA estimated the maximum use of streptomycin in citrus in the U.S., based on present citrus acreage, could result in 900,000 lbs being used each year. This would represent a more than 25-fold increase in the use of streptomycin used in plant agriculture. Yet EPA claims without sufficient justification such use would not cause undue risks to human health or the environment and does not consider this issue in the Proposed Interim Registration Review Decision (PID).

Assessment of Ecological Risks

EPA's environmental risk assessment is inadequate. The PID's 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 as well as spreading antibiotic resistance genes both through the environment and also to potential human pathogens. In addition, it also fails to adequately consider

[9] https://www.drugs.com/pro/streptomycin.html
[10] EPA 2018. Streptomycin Interim Registration Review Decision Case Number 0169. December 27, 2018. At: https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0687-0024

the potential impact of streptomycin on the microbiomes of animals and insects. We are particularly concerned about the inadequacy of EPA's consideration of effects on honey bees and the potential for the spread of antibiotic resistance genes.

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.[11] However, EPA's PID for streptomycin did not consider studies showing that antimicrobials can have an adverse effect on the honey bee microbiome, which could increase its susceptibility to disease.

Studies have increasingly shown that the gut microbiome can have complex effects on the health of an organism, including synthesis of vitamins, defense against pathogens, and modulation of behavior development, and immunity.[12] Use of antibiotics can greatly disturb the gut microbiome of humans and domesticated animals although both the numbers and diversity of bacteria in the gut.[13] Use of antibiotics has been associated with the appearance of resistant pathogens such as *Clostridium difficile*[14] and *Salmonella enterica*.[15]

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

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

[12] Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK and R Knight. 2012. Diversity, stability and resilience of the human gut microbiota. *Nature*, 489:220-230. At: https://cloudfront.escholarship.org/dist/prd/content/qt2n41h9pz/qt2n41h9pz.pdf?t=n4yswb

[13] Dethiefsen L, Huse S, Sogin ML and DA Relman. 2008. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PloS Biology,* 6:e280. At: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0060280

[14] Buffie CG, Jarchum I, Equinda M, Lipuma L, Govourne A et al. 2012. Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to *Clostridium difficile*-induced colitis. *Infection and Immunity* 80:62-73. At: https://iai.asm.org/content/iai/80/1/62.full.pdf

[15] Stecher B, R Robbiani, Walker AW, Westendorf AM, Barthel M et al. *Salmonella enterica* serovar typhimurium exploits inflammation to compete with the intestinal microbiota. *PLoS Biology*, 5:2177-2189. At: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0050244

[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

are visiting apple or pear flowers for nectar could be exposed to significant amounts of streptomycin.

There is also the possibility that honey bees could spread antibiotic resistance genes. Recent studies have found that many antibiotic resistance genes are on mobile elements, such as transposons, plasmids or integrons, which facilitate widespread movement of antibiotic resistance genes both within and between bacterial species, a process known as horizontal gene transfer.[17] Indeed, the transfer of resistance genes from one bacterial species to another is more frequent than previously known. A recently published study found that of all the genes in the human microbiome, over half of them have been the donor or recipient of horizontal transfer.[18] In addition, antibiotic resistance genes are more common in the environmental bacteria than previously thought and may be more mobile. Previously, it was thought that presence of antibiotic resistance genes resulted in a biological cost to maintain the resistance genes, so that the environment was viewed as a passive recipient of antibiotic resistance genes, which would reduce in frequency in the absence of an antibiotic. In fact, a 2017 study done in Argentina found that numerous resistance genes appear to not have a significant biological cost, suggesting that there is "an active role of the open environment as reservoir, recipient and source of antimicrobial resistance mechanisms, outlining an environmental threat."[19]

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 streptomycin in crop farming and dispersal of streptomycin-resistant genes."[20] The same study also noted that an identical Tn5393 had

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[17] Bag S, Ghosh TS, Banerjee S, Mehta O, Verma J et al. 2018. Molecular insights into antimicrobial resistance traits of commensal human gut microbiota. *Microbial Ecology*. At: https://www.researchgate.net/publication/326417311_Molecular_Insights_into_Antimicrobial_Resistance_Traits_of_Commensal_Human_Gut_Microbiota

[18] Jeong H, Arif B, Caetano-Anollés G, K KM and A Nasir. 2019. Horizontal gene transfer in human-associated microorganisms inferred by phylogenetic reconstruction and reconciliation. *Scientific Reports* 9:5953/ At: https://www.nature.com/articles/s41598-019-42227-5.pdf

[19] Chamosa LS, Alvares VE, Nardelli M, Quiroga MP, Cassini MH and D Centron. 2017. Lateral antimicrobial resistance genetic transfer is active in the environment. *Scientific Reports* 7 (Article number 513, 2017). At: https://www.nature.com/articles/s41598-017-00600-2.pdf

[20] 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

previously been identified in *E. coli* plasmid pVI-W9608, so clearly the Tn5393 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.

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 indicating that streptomycin is "practically nontoxic" to birds[21] and mammals.[22] 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,[23] birds,[24]

[21] Pg. 4 in EPA. 2018. *Op cit.*
[22] Pg. 5 in *Id.*
[23] 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
[24] 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[25] and terrestrial invertebrates[26] 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, or citrus fruits or leaves they eat, 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 addressed in the PID.

Antimicrobial Resistance Assessment

A major shortcoming of the PID is its failure to adequately assess the risk to human health caused by the potential of streptomycin use on plants to promote antibiotic resistance.

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, but does so in a flawed manner. EPA also primarily utilizes data from previous much more limited streptomycin usage in apples and pears, without assessing the impact of much larger potential uses in oranges and grapefruit. 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.[27] Finally, there should be an antimicrobial risk management strategy. There are deficiencies in how EPA carried out the framework at every stage.

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-

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[25]] 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

[26] 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

[27] 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

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, sometimes referring to resistance in the plant 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 "high" which appears justified.

For the exposure assessment, EPA estimates that exposure from consuming "pome fruits"--apples and pears--yields a rating of "medium."

In terms of the consequence assessment, EPA has determined that streptomycin is "highly important" since the drug 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 orchards affects the clinical efficacy of streptomycin or selects for multiple drug resistance.

With a release assessment of "high," 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" for apples and pears. 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 Interim Registration Review Decision (PID) 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 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 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, even treating all apple and pear trees in a single farm, 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.

Third, in terms of post-approval monitoring, EPA also falls short of what the FDA recommends in its risk assessment model. We urge EPA to require a monitoring method which is practical and feasible to carry out for all uses of streptomycin.

Transfer of Resistance

EPA's PID 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 integron). 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 a wide range of environmental and pathogenic bacteria "suggests that gene transfer events between human, animal, and plant-associated bacteria have occurred."[28] The Tn5393 transposon has been found frequently, and was first noted in the bacteria *Erwinia amylovora* that causes fire blight disease in apples and pears.[29] Another study also noted that an identical Tn5393 transposon had previously been identified in *E. coli* plasmid pVI-W9608, so clearly the Tn5393 transposon can transfer between distantly related bacteria, including plant pathogens and human pathogens.[30] A study in Italy that looked at 58 multidrug-resistant *Salmonella enterica* strains found that 84 percent of the streptomycin-

[28] 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

[29] 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

[30] Ludvigsen et al. 2018. *Op cit.*

resistant strains contained *strA-strB* genes.[31] 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."[32]

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.[33] 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.[34]

This problem is not adequately addressed in any of the EPA documents supporting its PID. We urge EPA to explicitly require monitoring, especially of *strA-strB* in TN5393, in Xcc, and other bacteria in the environment.

Concerns of FDA and CDC

EPA notes that there was concern from its federal partners, FDA and CDC, stating, "federal partners expressed several 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"[35] *italics* added. The restrictions that EPA propose in this PID do not appear to adequately address the concerns of FDA and CDC.

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[31] 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

[32] Pg.. 907 in *Id*

[33] 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

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

[35] Pg. 24 in EPA 2018 PID *Op cit.*

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. In the PID, EPA recognizes that the long-term use of streptomycin will clearly help select for resistance. EPA in fact will require a set of steps to help minimize the chance of resistance. EPA says they will require that streptomycin not be used in orchards in which the soil has been fertilized with animal waste/manure or human biosolids. We think this is a very good suggestion as a way to minimize transfer of streptomycin resistance genes to bacteria in the environment. EPA calls for using streptomycin as part of an integrated disease management (IDM) program, including 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. These are positive measures. EPA also calls for rotating streptomycin regularly 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.[36] We urge EPA to require that other methods of fighting this disease be employed as first choices.

Prevention of Drift

The PID recommends some positive improvements to the label regarding drift, including that spraying should only occur when the wind is below 10 mph, air-blast applications must not be made over the top of the canopy, and nozzles directed out of the orchard should be turned off in the outer two rows.

Although good advice, this nevertheless hardly prevents drift into neighboring fields or waters. Spraying of streptomycin into the canopy of trees is bound to result in drift. An option that would drastically reduce the environmental exposure, which EPA fails to recommend or require, 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

[36] 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.

oxytetracycline provided longer term control (6 to 8 months).[37] 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. The PID should state that any use should only be for trunk injection.

Worker Protection

As for the protection of workers spraying the antibiotic, the PID includes some new restrictions including that workers must wear gloves, protective eyewear, shoes and a respirator. Since this is not a restricted use pesticide, however, 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, in the PID, to, to classify streptomycin as a Restricted Use Pesticide.

Conclusion

The EPA's Proposed Decision would allow continued 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), and to human health (through promotion of antibiotic resistance), we urge EPA to cancel all uses of streptomycin in plant agriculture. Any approval for streptomycin use should require a lot more data. At a minimum EPA should classify streptomycin as a Restricted Use Pesticide so it can only be applied by a licensed trained applicator and only via trunk injection.

[37] 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