Consumer Reports Comments
on
EPA's Registration Review Proposed Interim Decisions for Several Pesticides:
Oxytetracycline
Docket No. EPA-HQ-OPP-2008-0686

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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 oxytetracycline 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, mandates 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 oxytetracycline fails to meet this standard. It states that, except for gauging the potential risks to threatened and endangered species, and the screening of oxytetracycline 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 oxytetracycline can still be used safely in

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plant agriculture, as long a few changes are made to help mitigate the risk of adverse impacts due to antimicrobial resistance. We disagree and urge EPA to prohibit tetracycline use based on its potential to adversely affect human health by promoting antibiotic resistance.

The PID for oxytetracycline focuses primarily on uses of oxytetracycline to treat fire blight (caused by *Erwinia amylovora*) and bacterial spot disease (caused by *Xanthomonas arbicola* pv *pruni*) in apple, pear, peach and nectarine. Presently, annual use of oxytetracycline on apples, pears and peaches is 16,800 lbs.[2] However, since 2016, EPA has authorized use of oxytetracycline on citrus crop group 10-10 in Florida to combat citrus greening (caused by *Candidatus liberibacter Asiaticus*) which attacks some 90% of citrus trees in Florida. EPA has authorized oxytetracycline to be sprayed on all citrus trees in Florida, up to three times a year. EPA estimated the maximum use of oxytetracycline in citrus in Florida, based on present citrus acreage, could result in 388,000 lbs being used each year. This would represent a more than 23-fold increase in the use of oxytetracycline used in plant agriculture. Yet EPA said such use would not cause undue risks to human health or the environment and does not consider the antibiotic resistance issue in the Proposed Interim Registration Review Decision (PID).

` We believe that continued use of oxytetracycline in apple, peach, pear and nectarine and, particularly, the large expansion in use in citrus in Florida 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, we think that EPA should phase out all uses of oxytetracycline in plant agriculture, particularly the new 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 decision to allow continued use of oxytetracycline on plant agriculture, particularly the large increase in use in citrus, 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. Oxytetracycline is classified by FDA as highly important in human medicine and is used to treat diseases caused by a range of bacteria, including *Chlamydia, Mycoplasma, Haemophilus, Rickettsia* spp., *Borrelia* and Spirochetes such as *Treponema*. Oxytetracycline can also be used to treat clostridial wound infections, anthrax and spirochete infections in patients that are sensitive to penicillins and/or macrolides.

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[2] EPA. 2018. Oxytetracycline: Proposed Interim Registration Review Decision Case Number 0655. At: https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0686-0027

EPA has also failed to adequately consider risks to non-target species, particularly honey bees. EPA did not evaluate oxytetracycline's potential 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 not to allow the use of this medically important antibiotic in plant production to combat plant diseases. If use is permitted, EPA should restrict application to injection of infected trees, rather than canopy spraying, so as to minimize environmental exposure. 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 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] Oxytetracycline, a tetracycline antibiotic, is classified by the US

[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

Food and Drug Administration (FDA) as highly important in human medicine.[8] It is used to treat diseases by a wide range of gram-negative and gram-positive bacteria, including *Chlamydia, Mycoplasma, Haemophilus, Rickettsia* spp., *Borrelia* and Spirochetes such as *Treponema*. Oxytetracycline can also be used to treat clostridial wound infections, anthrax and spirochete infections in patients that are sensitive to penicillins.[9]

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 the potential impact of oxytetracycline 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 oxytetracycline on pollinators, such as honey bees. EPA states that "[o]xytetracycline is classified as 'practically nontoxic' to honey bees on an acute exposure basis."[10] However, EPA's PID for oxytetracycline did not consider studies showing that antimicrobials can have an adverse effect on the honey bee gut microbial community (called the gut microbiome), which could increase the bee's susceptibility to disease.

Studies have increasingly shown that the gut microbiome can have complex effects on health of an organism, including synthesis of vitamins, defense against pathogens, and modulation of behavior development, and immunity.[11] Use of antibiotics can greatly disturb the gut microbiome of humans and domesticated

[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
[9] EPA. 2018. *Op cit.*
[10] Pg. 11 in *Id*
[11] 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

animals although both the numbers and diversity of bacteria in the gut.[12] Use of antibiotics has been associated with the appearance of resistant pathogens such as *Clostridium difficile*[13] and *Salmonella enterica*.[14]

A 2017 study found that tetracycline disrupted the gut microbiome of honey bees, causing declines in total microbial populations as well as having differential effects on the various gut bacterial species. Four of the eight major gut bacteria in honey bees were adversely affected by tetracycline, with the unexposed bees having five times more bacterial cells in the gut compared to those exposed to tetracycline.[15] Experiments found that exposure to tetracycline resulted in increased mortality for the bees both in the hive and in laboratory experiments in which bees were exposed to opportunistic bacterial pathogens. Another study found that the distinctive gut bacteria shared by honeybees and bumblebees appears to help protect against the trypanosome parasites.[16]

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

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[12] 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

[13] 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

[14] 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

[15] Raymann K, Shaffer Z and NA Moran. 2017. Antibiotic exposure perturbs 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

[16] Koch H and P Schmid-Hempel. 2011. Socially transmitted gut microbiota protect bumble bees against an internal parasite. *Proc. Natl. Acad. Sci. U.S.A.* 108:19288-19292. At: https://www.pnas.org/content/pnas/108/48/19288.full.pdf

[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

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]

A study published in 2012 found that long-term exposure to tetracycline has caused accumulation of resistance elements in the gut microbiota of honeybees. Using genomic techniques, the study found that samples from the gut of honeybees throughout the U.S, showed widespread presence of eight different tetracycline resistance genes, including efflux pump genes (*tetB, tetC, tetD, tetH, tetL,* and *tetY*) and ribosome protection genes (*tetM* and *tetW*), often at high frequencies.[20] In contrast, the gut microbiota of honeybees from Switzerland, the Czech Republic and New Zealand, where antibiotics have not been permitted in beekeeping, sometimes had very low levels of *tetB, tetC* or *tetW*, but lacked the other five tetracycline resistance genes. Furthermore, bees from four managed colonies in southern Arizona that were not treated directly with tetracycline nor been mixed with outside bees for over 25 years and samples from long-established feral colonies in Utah also had significantly lower copy numbers of tetracycline resistance genes, compared to other honeybees collected in the US. Since oxytetracycline has been used in the U.S. in plant agriculture for decades to treat fire blight and bacterial blight in apples, peaches, and pears and in beekeeping for the last 50 years, where it was used to treat foulbrood, caused by the bacteria *Paenibacillus lavrave* and *Melissococcus pluton*, this has "resulted in extensive tetracycline resistance in the gut microbiota."[21] Even though oxytetracyline was approved by FDA for use against foulbrood, EPA does not factor in the effect of that use when considering impacts of this drug's use in orchards on honeybees and other pollinators.

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[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] Tian B. Fadhil NH, Powell JE, Kwong WK and NA Moran. 2012. Long-term resistance to antibiotics has caused accumulation of resistance determinants in the gut microbiota of honeybees. *mBio* 3(6): eoo377-12. At: https://mbio.asm.org/content/mbio/3/6/e00377-12.full.pdf

[21] *Id*

Finally, the 2012 study also found that the resistance genes and mobile elements found in the U.S. honeybees were virtually identical to resistance gene in animal and human pathogens: "The tetracycline resistance that we observed in American samples reflects the capture of mobile resistance genes closely related to those known form human pathogens and agricultural sites."[22] Thus, it appears clear that the eight tetracycline resistance genes can easily move between bacteria in humans, animals and the environment. It is therefore possible that tetracycline resistance in environmental bacteria, including those in the honey bee gut microbiota, could be transferred to bacteria of human health concern. To minimize the possibility of transfer, EPA should consider phasing out use of oxytetracycline in plant agriculture.

Honey bees are major pollinators in US agriculture and are often shipped long distances to pollinate crops. The fact that the eight tetracycline resistance genes have move into gut bacteria of honey bees means that there is now the potential for widespread movement of these resistance genes between habitats due to shipment of honey bees for pollination purposes. EPA has not addressed this risk. EPA should not go forward with the PID without requiring significantly more data on effects on pollinators, especially the impact on gut microbiota, 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 PID states that oxytetracycline is "practically nontoxic" to birds[23] and mammals.[24] 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,[25] birds,[26] amphibians[27] and terrestrial

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[22] *Id*
[23] Pg. 4 in EPA. 2018. *Op cit.*
[24] Pg. 5 in *Id*
[25] 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
[26] 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
[27] 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*

invertebrates[28] can have negative health impacts on those organisms, and that antibiotics can cause disruption of microbiomes. Organisms that are living in the orchard ecosystem could encounter residues of oxytetracyline in the water they drink, or 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 oxytetracyline sprays will be affected and in particular how their microbiome might be affected. This data should all be considered 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 for oxytetracyline 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 carried this out in a flawed manner. EPA primarily utilizes data from previous much more limited oxytetracyline usage in apples and pears, where they have the usage data, without assessing the impact of much larger potential uses in oranges and grapefruit. Further, 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.[29] Finally, there should be an antimicrobial risk management strategy. There are deficiencies in how EPA carried out the framework at every stage.

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

[28] 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

[29] 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

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 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" based "on the known incidence of tetracycline resistance in clinical isolates, the movement of these resistance traits among bacteria of human health concern and the apparent selection pressure for oxytetracycline resistance presented by the existing treated acreage."[30] This appears justified.

For the exposure assessment, EPA estimates that exposure from consuming "pome fruits"--apples and pears-- yields a rating of "medium." Potential exposure from expanded use in citrus is not considered.

In terms of the consequence assessment, EPA has determined that it is "highly important" since oxytetracycline 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 apples, and pears affects the clinical efficacy of oxytetracycline 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." 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

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

could require professional application. If EPA rated the product as a Restricted Use Pesticide, only a licensed professional (trained) pest control operator could apply the pesticide. However, the PID does not call for it to be classified as a Restricted Use Pesticide; it states, rather that the label should say "Intended for use by professional applicators." Based on its GFI # 152 analysis we urge EPA to classify oxytetracycline, as a Restricted Use Pesticide.

Second, in terms of extent of use, even ignoring citrus uses, treating all apple, peach, pear or nectarine trees in an orchard would appear to constitute a "high" extent of use since, according to Table 7 in the GFI 152, "administration to flocks or herds of animals is defined as administration to all animals within a building, house, feedlot." Clearly, by analogy, treating all apple, peach, pear and nectarine trees in a single orchard, would appear to be a "high" extent of use. This classification has important implications for EPA's PID. According to Table 8, in the FDA risk management scheme, high extent of use should only be allowed for "low" risk antimicrobials, which oxytetracycline 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 consistent with present oxytetracycline use.

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 oxytetracycline.

Concerns of FDA and CDC

EPA notes that there was concern from its federal partners, FDA and CDC, stating, EPA's "federal partners expressed several concerns about the 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"[31] *italics* added. The restrictions that EPA proposes do not appear to adequately address the concerns of FDA and CDC.

Judicious Use

[31] Pg. 21 in *Id*

First, spraying of all trees (apple, pear or citrus) in an orchard 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 the label to state "Do not apply oxytetracycline in orchards in which the soil has been fertilized with animal waste/manure or human biosolids."[32] 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 oxytetracycline 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. These are positive measures.

EPA also suggests that oxytetracycline should be regularly rotated with other chemicals such as streptomycin 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.[33] Furthermore, tetracyclines and aminoglycosides (such as streptomycin) act on the same RNA site, which can also lead to cross-resistance. In addition, plasmids with multiple drug resistance genes are frequently found in many bacteria of human health concern and oxytetracycline/streptomycin resistance is a common trait on these plasmids.[34] Clearly the risk of cross resistance is a problem, since EPA states that consulting with "antibiotic experts from FDA, CDC and USDA on potential resistance concerns that might develop from the use of oxytetracycline on agricultural plants and it was concluded that such risk is possible and its probability is unknown at present."[35] In spite of this stated concern from their federal partners, EPA has not proposed requiring any detailed testing of bacteria on the apple, peach or pear trees for the presence of tetracycline resistance genes. We urge EPA to require that other methods of fighting this disease be employed as first choices and also require testing of environmental bacteria and bacteria on the trees, leaves and stems, looking for tetracycline resistance elements.

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[32] Pg. 22 in EPA. 2018. *Op cit.*

[33] 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.

[34] https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

[35] Pg. 17 in EPA. 2018. *Op cit.*

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, 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).[36] 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 oxytetracycline as a Restricted Use Pesticide.

Conclusion

The EPA's proposed decision would allow continued use of oxytetracycline, a highly important medical antibiotic, in the U.S. in plant agriculture. Given the importance of reducing antimicrobial resistance, and 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

[36] 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

cancel all uses of oxytetracycline in plant agriculture. Any approval for oxytetracycline use should require a lot more data. At a minimum EPA should classify oxytetracycline as a Restricted Use Pesticide so it can only be applied by a licensed trained applicator and only via trunk injection.