



Via Regulations.gov
March 14, 2019

The Honorable Andrew Wheeler
Administrator
U.S. Environmental Protection Agency
Office of Pesticide Programs Docket
Docket Center (28221T)
1200 Pennsylvania Ave. NW
Washington, D.C. 20460

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

Dear Administrator Wheeler:

Earthjustice, on behalf of the Farmworker Association of Florida, Farmworker Justice, Migrant Clinicians Network, and Environmental Confederation of Southwest Florida (ECOSWF), submits these comments opposing the new use registration of the pesticide product containing the active ingredient streptomycin sulfate for use on citrus crop group 10-10; citrus, dried pulp under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Farmworker Association of Florida, Farmworker Justice, and Migrant Clinicians Network are nonprofit organizations that champion the health and safety of thousands of farmworkers across the United States. ECOSWF is a non-profit confederation of organizations, corporations, groups, business entities, governmental agencies, and individuals devoted to the general purposes of conservation of the natural resources of Florida. We submit the following comments in particular to raise concerns about the human health risk assessment for streptomycin sulfate on which the EPA's proposed registration decision relies.

The EPA's Streptomycin Human Health Risk Assessment (Risk Assessment) is inadequate and the EPA cannot rely on this assessment to determine that streptomycin meets the standards for registration under FIFRA. The Risk Assessment is inadequate for the following reasons:

- 1) EPA erroneously waived all toxicological data requirements based on streptomycin's history of use as a human drug;
- 2) EPA did not adequately assess the carcinogenicity of streptomycin, in part because it waived all toxicological data requirements;

- 3) EPA failed to apply the 10x safety factor as required under the Food Quality Protection Act to account for potential pre-and post-natal toxicity and incompleteness of the data with respect to exposure and toxicity to infants and children;
- 4) EPA failed to seriously consider the increased exposure and risk to farmworkers and their families in the Risk Assessment, in violation of FIFRA, EPA policy, and Executive Order 12,898; and
- 5) The Risk Assessment does not adequately analyze the potential for increased antibiotic resistance from the use of streptomycin on citrus crops, nor does it adequately analyze cumulative potential risks of streptomycin and oxytetracycline.

We strongly urge EPA to deny the registration application for streptomycin, or at the least, revise the Risk Assessment to correct these inadequacies and legal errors and reconsider its conclusions on the basis of the corrected information.

BACKGROUND

As defined by EPA, a registration review decision “is the Agency’s determination whether a pesticide meets, or does not meet, the standard for registration under FIFRA.¹ A pesticide meets this standard if, and only if, EPA finds that it does not cause “unreasonable adverse effects on the environment,”² which FIFRA defines to include “any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide[.]”³

EPA determines whether a pesticide meets this standard in part through a human health risk assessment that identifies the potential adverse health effects caused by the pesticide, derives levels of concern, and estimates whether levels of exposure exceed the levels of concern.⁴ If a pesticide does not meet this standard, EPA will deny, revoke or modify the pesticide’s registration.⁵ In conducting this analysis, EPA must address the *total* risk presented by *all*

¹ 40 C.F.R. § 155.57.

² 7 U.S.C. § 136a(5).

³ 7 U.S.C. § 136(bb).

⁴ See generally EPA, *Assessing Human Health Risk from Pesticides*, <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/assessing-human-health-risk-pesticides> (last visited Mar. 14, 2019) (“We use risk assessments to make informed decisions...during our regular review of existing pesticides.”).

⁵ See *id.* (“When our assessments show that risks from a pesticide need to be reduced, we modify where and how it can be used. If a pesticide does not meet our safety standard, after considering all appropriate risk reduction measures, we will not allow it to be used.”).

exposures in *all* people. Failure by EPA to do so violates FIFRA and would be an arbitrary and capricious agency action.⁶

Further, EPA must adhere to the requirements of Executive Order 12,898 when conducting human health risk assessments. Executive Order 12,898 directs federal agencies to “achiev[e] environmental justice by identifying and addressing ... [the] disproportionately high and adverse human health or environmental effects of [their] programs, policies, and activities on minority populations and low income populations.”⁷ EPA has committed to incorporating environmental justice into its policies, programs, and rulemaking.⁸

Specifically, FIFRA mandates that EPA protect the health of farmworkers. Indeed, the “entire purpose of the [1970 revisions to FIFRA, known as the Federal Environmental Pesticide Control Act (FEPCA)] is to protect man and the environment,” and farmers and farmworkers are “the most obvious object of th[at] bill’s protection.”⁹ At the time of FEPCA’s passage, one Senate Committee asserted that FEPCA “provides complete safeguards to protect farmers and others coming into contact with pesticides or residues.”¹⁰ The Risk Assessment disparately treats farmworkers — who are predominantly Latinx and low-income.¹¹ Farmworkers are the primary handlers of pesticides and use them in the course of their work. The Risk Assessment disparately treats farmworkers as compared to predominantly middle class, white non-agricultural workers who are exposed to the same or similarly toxic chemicals by neglecting farmworkers non-

⁶ 5 U.S. C. § 706 (2).

⁷ Exec. Order No. 12,898, 59 Fed. Reg. 7,629 (Feb. 11, 1994).

⁸ See EPA, EPA-300-B-1-6004, *EJ 2020 Action Agenda: The U.S. EPA’s Environmental Justice Strategic Plan for 2016 – 2020*, 1 (Oct. 2016), https://www.epa.gov/sites/production/files/2016-05/documents/052216_ej_2020_strategic_plan_final_0.pdf (“By 2020, we envision an EPA that integrated environmental justice into everything we do.”); *id.* at 13. (“Further integrating environmental justice (EJ) in EPA’s core rulemaking function is essential[.]”).

⁹ *Organized Migrants in Cmty Action, Inc. v. Brennan*, 520 F.2d 1161, 1168-69 (D.C. Cir. 1975), quoting S. Rep. No. 92-838, at 43, 44 (1972), reprinted in 1972 U.S.C.C.A.N. at 4063.

¹⁰ *Id.* at 1168, 1169 (“If there is any question as to whether [farmers and farmworkers] are fully protected, we do not know what it could be.”).

¹¹ In addition to farmworkers from Mexico and Central America, in Florida there are many Haitian farmworkers and across the country there are an increasing number of farmworkers from indigenous communities (many from Central America) who only speak their indigenous languages and may have little or low literacy rates, which contributes to their understanding of labels and other protection, such as Personal Protective Equipment (PPE). See William Kandel, U.S. Dept. Agric., *Profile of Hired Farmworkers, A 2008 Update* at 8-9, 25-27 (July 2008), <https://www.ers.usda.gov/webdocs/publications/46038/err-60.pdf?v=0>; see also Erin Sologaistoa, Fla. Ass’n of Cmty. Health Ctrs., *Farmworkers in the Southeast: Alabama, Florida, Georgia, Mississippi* 13-14 (Nov. 2011), <https://fachc.memberclicks.net/assets/docs/Farmworkers%20in%20the%20Southeast.pdf>.

occupational exposure to streptomycin in its Risk Assessment. This violates EPA's obligations and commitments.

Streptomycin is an antibiotic of the aminoglycoside class. The World Health Organization considers aminoglycoside antibiotics to be "critically important to human medicine" because they are "the sole, or one of limited available therapies, to treat serious bacterial infections in people."¹² It was the first aminoglycoside antibiotic to be discovered and has seen widespread use as an injectable drug since its discovery in 1943. Streptomycin is often still used as a secondary drug treatment for tuberculosis, as well as other bacterial infections. Another aminoglycoside, gentamicin, is typically used in combination with a penicillin or cephalosporin for treatment of severe infections caused by *E. coli*, *Staphylococcus aureus*, *Enterobacter*, *Klebsiella*, *Serratia*, *Pseudomonas aeruginosa*, and other gram-negative bacteria that have developed resistance to less toxic antibiotics.¹³ Gentamicin is most commonly used for septicemia, bacterial endocarditis, peritonitis, meningitis, pelvic inflammatory disease, and pneumonia.¹⁴ Gentamicin was first approved for use in the United States in 1970 and remains in wide use.¹⁵

In 2016, the manufacturers submitted a petition to request the EPA to establish a tolerance for streptomycin on citrus crop group 10-10¹⁶ to manage Huanglongbing (HLB) disease, which is also referred to as citrus greening, and citrus canker.¹⁷ HLB is caused by the plant bacterial pathogen *Candidatus Liberibacter asiaticus* (Clas) and is transmitted into the citrus tree phloem by the Asian citrus psyllid, an invasive insect. Citrus greening is a serious problem affecting citrus growth across the country and particularly in Florida.¹⁸ Streptomycin will be applied via airblast equipment.¹⁹ As the EPA acknowledges, the use of streptomycin will not be effective in curing HLB, but rather will be used to control the insect vector in the hopes of reducing transmission of the disease. Only copper products have been used to treat the disease itself.²⁰ In fact, the EPA's Review of Benefits includes data that only by the *second year* of treatment, HLB-infected oranges and grapefruit trees were less infected.²¹ Moreover, the EPA acknowledges that the pathogens

¹² WHO, *Critically Important Antimicrobials for Human Medicine 5th Revision* (2016) at 8, 21, <https://apps.who.int/iris/bitstream/handle/10665/255027/9789241512220-eng.pdf>.

¹³ National Institutes of Health, Drug Record Gentamicin, <https://livertox.nih.gov/Gentamicin.htm> (last updated October 30, 2018).

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ Citrus Group 10-10 includes all commercial citrus fruit such as grapefruit, lemon, lime, orange, tangelo, tangerine, citrus citron, kumquat, pummelo, and various citrus hybrids. See EPA, Proposed Registration Decision at 15, Dkt. EPA-HQP-OPP-2016-0067-0023.

¹⁷ See University of Florida/Institute Food and Agricultural Sciences, 2014 *UF/IFAS Research Discoveries 2*, <https://research.ifas.ufl.edu/docs/pdf/featured-discoveries/RD-citrusgreening.pdf>.

¹⁸ Proposed Registration Decision at 14.

¹⁹ EPA, Risk Assessment at 12, Dkt. EPA-HQP-OPP-2016-0067-0020.

²⁰ *Id.* at 15.

²¹ EPA, Review of Benefits at 8-9, Dkt. EPA-HQP-OPP-2016-0067-0010.

causing HLB and citrus canker are not eliminated by streptomycin treatment and require continued long-term disease management. Thus, the use of streptomycin may help with some infected citrus, but is not in itself the cure for citrus canker or HLB. The existing data demonstrates that long-term use of streptomycin is required and will likely lead to increased streptomycin resistance.²²

A major concern raised by the use of streptomycin and other antibiotics as pesticides is the development of antibiotic resistance in bacterial pathogens that infect humans. Antibiotic resistance is an increasingly serious and life-threatening public health crisis.²³ The World Health Organization has warned that we are rapidly approaching a “post-antibiotic” era in which antibiotics used to treat common infections no longer work.²⁴ This would mean “an end to modern medicine as we know it.”²⁵ The Centers for Disease Control and Prevention (CDC) estimate that, every year, antibiotic-resistant bacteria infect at least two million people in the U.S. and kill 23,000 of them.²⁶

The use of antibiotics — whether as pesticides or as drugs — drives the development of antibiotic resistance. In a bacterial population, certain bacteria become *resistant* to an antibiotic when they develop genes that enable them to survive exposure to the drug.²⁷ Other *susceptible* bacteria do not.²⁸ When the population is exposed to the antibiotic, the resistant bacteria survive

²² See University of Florida/Institute Food and Agricultural Sciences, *Combatting Bacterial Spot on Tomatoes and Peppers* (last modified Oct. 30, 2016), <https://research.ifas.ufl.edu/main-menu-tab/research/greatest-ufifas-unit-accomplishments/combating-bacterial-spot-on-tomatoes-and-peppers/> (“UF/IFAS researchers have led the charge against bacterial spot for the past 50 years, and their research has made a major impact on basic biology and disease management practices. This included the first documentation in a field setting of a bacterial pathogen showing resistance to the antibiotic streptomycin, resulting in growers using alternative control strategies.”).

²³ See e.g., WHO, *Antibiotic Resistance Factsheet*, Feb. 5, 2018, <https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance>; See, e.g., Centers for Disease Control and Prevention, *National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS)*, <https://www.cdc.gov/narms/faq.html> (last visited Mar. 14, 2019); Wolfgang Witte, *Medical Consequences of Antibiotic Use in Agriculture*, 279 *Sci.* 996, 996-97 (Feb. 1998) (detailing empirical results suggesting “that antibiotic use in animal husbandry is a driving force for the development of antibiotic resistance in certain pathogenic bacterial species.”).

²⁴ Margaret Chan, *Antimicrobial Resistance in the European Union and the World* (Mar. 14, 2012), http://www.who.int/dg/speeches/2012/amr_20120314/en.

²⁵ *Id.*

²⁶ Centers for Disease Control and Prevention, *Antibiotic/Antimicrobial Resistance (AR/AMR)*, <https://www.cdc.gov/drugresistance/> (last visited Mar. 13, 2019).

²⁷ CDC, *Antibiotic Resistance Threats in the United States, 2013* (Apr. 23, 2013), <https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>.

²⁸ *Id.*

and reproduce, giving rise to additional resistant bacteria, while the susceptible bacteria perish.²⁹ The use of antibiotics is what exposes bacterial populations to antibiotics.³⁰ According to the CDC, antibiotic use “is the single most important factor leading to antibiotic resistance around the world.”³¹ As the CDC warns, “[t]he more that antibiotics are used today, the less likely they will still be effective in the future.”³² The use of streptomycin as a pesticide will lead to streptomycin resistance in bacterial pathogens, reducing the effectiveness of streptomycin as a human drug.

EPA’s proposed registration approval for streptomycin would add to the already pervasive use of antibiotics in our food supply and their presence in the environment. In December 2018, the EPA approved the registration of oxytetracycline for use on citrus crops, and only months later is now considering registering streptomycin as an additional citrus antibiotic.³³ Concentrated animal feeding operations (CAFOs) are also major sources of antibiotic use because every major industrial animal category (swine, poultry, and cattle) routinely administers sub-therapeutic and/or growth promoting antibiotics in daily feed and water.³⁴ Eighty percent of antibiotics sold in the U.S. in 2010 were used for livestock, mostly for nontherapeutic purposes.³⁵ Studies estimate that about 75 percent of antibiotics used in animals are not absorbed by the animal, but instead are passed to waste that is applied to agricultural land.³⁶ Following land application, the antibiotics can enter water bodies. In a recent nationwide study of stream sites, maximum antibiotics concentrations ranged from 12 nanograms per liter up to 1.8 micrograms per liter (parts per billion), with many sites hosting multiple antibiotics.³⁷ Concentrations of just 0.5 micrograms per liter have been shown to change aquatic microbial communities.³⁸ One risk of these microbial changes is that the antibiotics suppress beneficial bacteria in the water, thereby harming aquatic organisms that rely on healthy levels of “good” bacteria.³⁹

Beyond the individual concerns about chronic human consumption of low levels of antibiotics in drinking water, aquatic antibiotic pollution poses the most substantial health threat

²⁹ *Id.* at 14.

³⁰ *Id.* at 41.

³¹ *Id.* at 11.

³² *Id.* at 41.

³³ EPA, Oxytetracycline: Pesticide Tolerances, 83 Fed. Reg. 62489 (Dec. 4, 2018) (codified at 40 C.F.R. Pt. 180).

³⁴ Joanne Chee-Sanford et al., *Fate and Transport of Antibiotic Residues and Antibiotic Resistance Genes Following Land Application of Manure Waste*, 38 J. Env'tl. Quality 1086 (2009).

³⁵ Jerome A. Paulson et al., *Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics* 136 American Academy of Pediatrics 6, e1670 (Nov. 16, 2015).

³⁶ Chee-Sanford et al., *supra* n. 34.

³⁷ Paul M. Bradley et al., *Expanded Target-Chemical Analysis Reveals Extensive Mixed-Organic-Contaminant Exposure in U.S. Streams*, Env'tl. Science & Tech. 4792, 4799 (Apr. 2017).

³⁸ *Id.*

³⁹ James P. Meador et al., *Contaminants of Emerging Concern in a Large Temperate Estuary*, Env'tl. Pollution 264 (June 2016).

to humans because it increases the rate of antibiotic resistance. Studies have linked pharmaceutical water pollution to the growth of antibiotic resistance, including a recent study which found that current antibiotic levels in water could inhibit some naturally occurring and potentially beneficial bacteria and trigger some antibiotic resistance.⁴⁰

ARGUMENT

EPA's Risk Assessment for streptomycin cannot support the Proposed Registration Decision under FIFRA and does not comply with the EPA's policy implementing Executive Order 12,898. For the following reasons, we respectfully request that EPA deny the proposed registration, or at the least, revise the Risk Assessment and fix the flaws identified below.

1. EPA erroneously waived all toxicological data requirements based on streptomycin's history of use as a human drug.

EPA takes the facially absurd position that because streptomycin has seen historical medicinal use, the Agency may waive all toxicological data requirements.⁴¹ The Risk Assessment concludes "that additional toxicity data are not required for streptomycin because the available laboratory animal toxicity data, in conjunction with the conclusions that can be drawn from the decades of use of streptomycin as a human antibiotic drug without significant incidents, is sufficient to assess the safety of streptomycin; therefore, additional toxicity data have been waived by the agency."⁴² However, the history of streptomycin use in humans does reveal that "[c]hildren born to mothers treated with streptomycin injections at therapeutically-relevant doses have sometimes had hearing loss."⁴³

Additionally, injections of streptomycin as a drug can cause inner ear toxicity resulting in vestibular problems with loss of balance or equilibrium and hearing loss, as well as reversible

⁴⁰ See, e.g., *id.* at 263-64; Mitchell S. Kostich et al., *Concentrations of Prioritized Pharmaceuticals in Effluents From 50 Large Wastewater Treatment Plants in the US and Implications for Risk Estimation*, 184 *Env'tl. Pollution* 354, 355 (2014); Bradley et al., *supra* n. 36 at 4799 (for example, the common antibiotic ciprofloxacin, was found at about a quarter of studied stream sites across the country at concentrations up to 400 nanograms per liter — when ciprofloxacin is at levels of only 100 nanograms per liter it is found to select resistant bacteria); see also Louise Chow et al., *Potential Impacts of Aquatic Pollutants: Sub-clinical Antibiotic Concentrations Induce Genome Changes and Promote Antibiotic Resistance*, *Front. Microbiol.* 6:803 at 8 (Aug. 2015) ("Very small concentrations of common antibiotics can induce significant genotypic and phenotypic changes in bacterial species. Given the huge quantities of antibiotics that are entering the environment, it is likely that this antibiotic pollution is generating antibiotic resistant organisms that may be a source of newly emerging opportunistic pathogens.").

⁴¹ Risk Assessment at 13.

⁴² *Id.*

⁴³ *Id.* at 14.

kidney toxicity.⁴⁴ EPA cannot support its decision to waive *all* toxicological data requirements, including data on developmental toxicity, when the long history of streptomycin as a drug in humans does demonstrate potential adverse health effects.

Further, EPA fails to take into account the potential risks posed by chronic exposure to low levels rather than the known risks posed by short-term exposure to high levels of streptomycin when it is used as a drug. For example, EPA derives the reference dose and population adjusted dose for chronic dietary exposure from the two-year rat study.⁴⁵ (These doses are the same because the FQPA safety factor was reduced from 10x to 1x.) However, had the Agency required additional toxicity studies that appropriately characterize hazards associated with chronic exposure, it may have identified a lower point of departure than the NOAEL (no observed adverse effect level) from the two-year rat study. The EPA cannot waive all toxicological data requirements for chronic toxicity studies based merely on the history of using streptomycin as a human drug, when that history can only characterize the effects of acute or short-term exposure.

2. EPA did not adequately assess the carcinogenicity of streptomycin, in part because it waived all toxicological data requirements.

Similarly, the EPA did not adequately assess the potential carcinogenic effects of streptomycin because it waived all toxicological data requirements. The Risk Assessment states “[t]here is not enough information to classify the carcinogenic potential of streptomycin since guideline carcinogenicity studies are not available.”⁴⁶ These studies are only unavailable because the data requirements were waived. Within the same paragraph, the Risk Assessment acknowledges that a two-year rat carcinogenicity study used by the FDA and World Health Organization (WHO) is available and did not demonstrate evidence of carcinogenicity – “although limited histopathology was reported,” but acknowledges that a mouse carcinogenicity study is not available for streptomycin.⁴⁷ The EPA clearly does not believe that carcinogenicity can be ruled out given the two-year rat study and its use by the FDA and WHO in setting

⁴⁴ *Id*; See generally Adebolajo A. Adeyemo et al., *Study of Streptomycin-Induced Ototoxicity: Protocol for a Longitudinal Study*, SpringerPlus (2016) 1, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4912548/pdf/40064_2016_Article_2429.pdf; Erol Selimoglu, *Aminoglycoside-Induced Ototoxicity*, 13 *Current Pharmaceutical Design* 119-124 (2007); Young Hyo Kim, et al., *Clinical Evaluation and Early Diagnosis of Streptomycin Ototoxicity*, 7 *J. Int’l Advanced Otology* 91, 92-94 (Jan. 2011), <http://www.advancedotology.org/sayilar/76/buyuk/15-Kim.pdf>; P. de Jager & R. van Altena, *Hearing Loss and Nephrotoxicity in Long-Term Aminoglycoside Treatment in Patients with Tuberculosis*, 6 *Int’l J. of Tuberculosis and Lung Disease* 622, 622-23, 626 (Apr. 2002), <https://www.ingentaconnect.com/content/iatld/ijtld/2002/00000006/00000007/art00012#>.

⁴⁵ Risk Assessment at 16, Table 4.5.4.

⁴⁶ *Id.* at 16.

⁴⁷ Risk Assessment at 16.

tolerances for streptomycin in animal drug residue, given its conclusion that “there is not enough information.”⁴⁸

The EPA also states that a literature search for streptomycin toxicity in animals and humans did not result in data with evidence of carcinogenicity. That the EPA’s literature search did not affirmatively return evidence of carcinogenicity does not permit the Agency’s speculative assumption that there must be no risk of carcinogenicity.⁴⁹ Due to streptomycin’s historic use as a short course treatment in humans, researchers would likely not be interested in a study assessing cancer risk associated with chronic exposure to streptomycin because it was not administered in long-term doses. However, that does not negate the importance in assessing the risks of chronic dietary exposure to consumers, and prolonged, more frequent exposure to farmworkers and their families.

3. EPA failed to apply the 10x safety factor as required under the Food Quality Protection Act (FQPA) to account for potential pre-and post-natal toxicity and incompleteness of the data with respect to exposure and toxicity to infants and children.

In 1996, Congress amended the Food, Drug, and Cosmetics Act (FDCA) by enacting the Food Quality Protection Act (FQPA), Pub.L. No. 104–170, 110 Stat. 1489. The FQPA directs the EPA to ensure with “reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.”⁵⁰ The FQPA requires EPA to give special consideration to risks posed to infants and children when establishing pesticide tolerances. Specifically, the FQPA directs the EPA to apply an additional tenfold or 10x margin of safety to take into account the potential pre-and post-natal toxicity and completeness of data (or lack thereof) with respect to exposure and toxicity to infants and children.⁵¹ This 10x child safety factor is presumptively applied to all pesticide tolerances. Thus, in making registration and tolerance decisions, the EPA must assume that the risk to children from the use of a particular pesticide on food is 10 times greater than for adults.⁵² The EPA may deviate from the 10x margin of safety, if on the basis of reliable data, the alternate margin will be safe enough for infants and children.⁵³

In *NCAP v. E.P.A.*, the EPA concluded that the toxicological data for several pesticide registrations showed no evidence of increased sensitivities for developing fetuses and the young.

⁴⁸ *Id.*

⁴⁹ *Id.* at 20 (“A cancer dietary exposure and risk assessment was not conducted since streptomycin is not likely to be carcinogenic to humans.”).

⁵⁰ 21 U.S.C. § 346a(b)(2)(A)(ii).

⁵¹ 21 U.S.C. § 346a(b)(2)(C).

⁵² Risk Assessment at 20; *Nw. Coal. for Alternatives to Pesticides (NCAP) v. E.P.A.*, 544 F.3d 1043, 1046 (9th Cir. 2008).

⁵³ 21 U.S.C. § 346a(b)(2)(C).

The Court in reviewing the Agency's actions for compliance with the FQPA determined that the Agency did not explain the connection between the toxicological data and the 3x safety factor the Agency applied in lieu of the presumptive 10x safety factor.⁵⁴ The Court found that it was entirely unclear why the EPA chose a 3x safety factor as opposed to 4x or 9x or any other safety factor.⁵⁵ The Court held that the EPA arbitrarily lowered the safety levels while maintaining certain concerns about each pesticide considered, but without pointing to specific evidence for the safety levels applied.⁵⁶

Here, the EPA has arbitrarily applied a lower safety factor — in fact no safety factor for infants and children — without adequately explaining its decision to apply a 1x safety factor versus the presumptive 10x. In discussing the safety factor for infants and children, the Risk Assessment explains:

No teratogenic effects were noted in a rabbit developmental study at the high dose of 10 mg/kg/day. Children born to mothers treated with streptomycin injections at therapeutically relevant dose levels have sometimes had hearing loss; no teratogenic effects have been attributed to streptomycin treatment. Because the dose selected for risk assessment is much lower than the injected dose at which toxicity occurs in humans, and at the levels of exposure anticipated due to pesticidal uses, there is no indication of neurotoxicity or susceptibility, and there are no residual concerns, the FQPA safety factor was reduced to 1x.⁵⁷

The EPA inadequately justified its decision to reduce the presumed 10x safety factor to 1x, and asserted, in the same sentence, that while there are no teratogenic effects attributed to streptomycin, there are however, risks to children born to mothers treated with streptomycin. Thus, EPA has acknowledged — but disregarded — that there *are* potential risks associated with prenatal exposure to streptomycin.

The EPA tries to explain that because the pesticidal uses are anticipated to be at lower doses than a streptomycin injection for treatment, that there is no indication of neurotoxicity or susceptibility. However, that statement lacks a scientific basis. As the EPA waived all toxicological data requirements, it can point to no factual basis for its conclusion that the lower doses will not elicit similar or different toxicities. Moreover, there is available data to indicate that prenatal exposure is associated with hearing loss. Therefore, the “reliable data” required under FQPA to justify a decision to lower the safety factor from 10x, does not actually support a lesser margin of safety.

⁵⁴ *NCAP v. EPA* at 1052.

⁵⁵ *Id.*

⁵⁶ *Id.*

⁵⁷ Risk Assessment at 14.

Furthermore, the reduction to 1x for the FQPA safety factor has another practical effect on the EPA's conclusions regarding the safety of streptomycin. As discussed above, the EPA used the two-year rat study to determine the reference dose and population adjusted dose for chronic dietary exposure. The Risk Assessment's Table 5.4.6 presents the estimates of chronic dietary exposure by age group and compares them to the chronic population adjusted dose (cPAD) to determine the risk.⁵⁸ For example, in infants less than 1 year of age, the exposure estimate (0.045572 mg/kd/day) divided by the cPAD (0.05 mg/kg/day; see Table 4.5.4) is 0.91 or 91 percent.⁵⁹ Because all of the exposure estimates are thus less than 100% of the cPAD, the Agency concluded that "risks are below the level of concern."⁶⁰ However, had EPA not reduced the FQPA safety factor from 10x to 1x, the cPAD would be 0.005 (as opposed to 0.05) and the exposure estimate would in fact be 911% of the cPAD. Thus, streptomycin would not meet the safety standard.⁶¹ Furthermore, if EPA had required a chronic toxicity study and the NOAEL from the additional study was 4/mg/kg/day instead of the 5 mg/kg/day observed in the two-year rat study, the cPAD would be 0.04 *even if* the FQPA safety factor was only 1x. In this example, the exposure estimate would be nearly 114% of the cPAD and streptomycin would not meet the safety standard.

4. EPA failed to seriously consider the increased exposure and risk to farmworkers and their families in the Risk Assessment, in violation of FIFRA, EPA policy, and Executive Order 12,898.

The EPA's Risk Assessment does not adequately take into account what exposure to farmworkers looks like when dietary exposure is combined with occupational exposure. The issues explained above regarding the waiver of all toxicological data and the FQPA safety factor, not only affect consumers, but also affect farmworkers and their families. Additionally, farmworkers are obviously at an increased exposure level compared to the general population, as they are the pesticide handlers, work in the citrus groves after application of streptomycin and other pesticides/antibiotics, and are also exposed to dietary and residential exposures.

The Risk Assessment finds that for proposed uses of streptomycin, all of the scenarios result in margins of exposure (MOE) that are not of concern (i.e., $MOE \geq LOC = 100$) with "label-required personal protective equipment (PPE; use of a dust/mist respirator)."⁶² The Risk Assessment reports that these "MOEs range from 3,400 to 31,000 with the use of a PF5 respirator."⁶³ Here, EPA relies on unsupported assumptions about the use of personal protective equipment (PPE) to conclude that occupational exposures do not pose risks of concern to occupational handlers. The Agency assumes that the handlers will be wearing the label-specified

⁵⁸ *Id.* at 20.

⁵⁹ *Id.* at 19-20.

⁶⁰ *Id.* at 20.

⁶¹ *Id.* at 19-20

⁶² *Id.* at 26.

⁶³ *Id.*

PPE, which includes wearing long sleeved shirt, long pants, chemical-resistant gloves, shoes plus socks, and a dust/mist respirator. EPA does not identify a factual basis for this assumption. In fact, the available evidence is to the contrary, demonstrating that pesticide handlers frequently do not use PPE, often for reasons beyond their control. For example, in a study of 220 randomly selected dairy farmers interviewed after pesticide application, less than 15 percent complied with the gear use requirements and that, for three pesticides applied, the proportions using none of the required gear were 56.9 percent, 38.6 percent, and 47.5 percent.⁶⁴ A survey of grain farm operators in central Ohio, found that more than 40 percent saw no need for PPE during pesticide application operations.⁶⁵ Similarly, in Minnesota, 44 percent of farm operators did not wear chemically resistant gloves, and 78 percent did not wear other protective gear, at least three quarters of the time when handling pesticides.⁶⁶

A registration review decision under FIFRA requires the EPA to determine whether a pesticide poses “any unreasonable risk.”⁶⁷ EPA’s exclusion of non-occupational exposures from the occupational risk assessment results in the underestimation of risk, since the workers who sustain occupational exposure are also exposed to pesticides as consumers and residents in areas where pesticides are applied. EPA cannot appropriately determine whether a pesticide meets the standard set by FIFRA if the Agency does not consider aggregate exposure by combining food, drinking water, residential, and occupational exposures. EPA also fails to adequately assess certain exposures that place farmworkers and their families at even greater risk. These exposures include pesticide residues on boots, tools, work clothes, and skin of family members who handle pesticides or work in areas where they are applied and then return home (“take-home” exposures).⁶⁸ Exposure may also be present from soil and drift through the air into farmworker’s homes, schools, and playgrounds.⁶⁹ In the Risk Assessment, EPA does not assess the take-home exposures or assess the risks they pose to farmworkers and their families.

⁶⁴ Melissa J. Perry et al., *Compliance with Required Pesticide-Specific Protective Equipment Use*, 41 *Am. J. Indus. Med.* 70, 70-71 (Jan 2002).

⁶⁵ David H. Pedersen et al., *Agricultural Hazard Data from a Population-Based Survey of Cash Grain Farms: Ohio Observations*, 14 *Applied Occupational & Env'tl. Hygiene* 299, 304 (1999).

⁶⁶ Jeffrey H. Mandel et al., *Factors Associated with Safe Use of Agricultural Pesticides in Minnesota*, 12 *J. Rural Env'tl. Health* 301, 303 (1996).

⁶⁷ 7 U.S.C. §§ 136(bb), 136a(c).

⁶⁸ Chensheng Lu et al., *Pesticide Exposure of Children in an Agricultural Community: Evidence of Household Proximity to Farmland and Take Home Exposure Pathways*, 84 *Env'tl. Res.* 290, 290-91 (2000).

⁶⁹ Nat'l Res. Council, *Pesticides in the Diets of Infants and Children* 308-09 (1993), <https://www.ncbi.nlm.nih.gov/books/NBK236275/>; see e.g., Soren Thiele-Bruhn, *Pharmaceutical Antibiotic Compounds in Soils — A Review*, 166 *J. Plant Nutri. Soil Sci.* 145 (2003) (discussing antibiotics in soil and degradation).

Additionally, the Risk Assessment does not even attempt to assess the dermal risk associated with streptomycin.⁷⁰ The EPA concluded:

[b]ecause oral absorption of aminoglycosides related to streptomycin is less than 1% and because the skin has a protective barrier role compared to the lining of the GI tract, dermal absorption *should be much less* than by the oral route. . . [so] toxicity by the dermal route at environmental concentrations is not expected. Therefore, quantitation of risk following dermal exposure was not required.⁷¹

This conclusion is unsupported. As described above, EPA waived all of the toxicological data requirements. It does not appear the agency has considered any data on the effects of dermal absorption of streptomycin and therefore it cannot conclude that such effects will not occur. In fact, the EPA does not even address the potential issue of allergic reactions based on dermal or eye exposure in acute or chronic exposure.

Allergic reactions on the skin and eyes following dermal exposure to streptomycin have been reported since the 1940s. In a 1949 article, a researcher reviewed 3 case studies of nurses/hospital workers who had exposure to streptomycin injections and presented with rashes on their fingers, eyes, face, and upper body.⁷² One case study reported troubling breathing due to nasal swelling. The paper concluded that streptomycin sensitivity does exist and develops in certain individuals who have frequent contact with solutions of the drug, and that development of skin sensitivity to streptomycin is due to frequent contact over a period of several weeks.⁷³ Another journal article from 1951 similarly concluded that “[h]ypersensitivity to streptomycin is a fairly common occurrence in patients receiving the drug and in personnel preparing and administering it. It is relatively much commoner in people who handle the drug than in those who receive it.”⁷⁴ Additionally, the proposed label for streptomycin says “harmful if absorbed through skin.”⁷⁵ And yet, the EPA did not even attempt to analyze the potential dermal exposure risks for farmworkers handling streptomycin, for farmworkers in the groves after application of streptomycin, or for farmworker families exposed through take-home exposures.

⁷⁰ Risk Assessment at 26 (“As dermal risk is not quantitatively assessed, routes of exposure are not combined.”).

⁷¹ Risk Assessment at 15.

⁷² S. William Simon, *Skin Sensitivity to Streptomycin*, 20 J. Allergy & Clinical Immunology 56, 56-60 (Jan. 1949), [https://www.jacionline.org/article/0021-8707\(49\)90083-0/pdf](https://www.jacionline.org/article/0021-8707(49)90083-0/pdf).

⁷³ *Id.* at 57.

⁷⁴ Archibald C. Cohen & George C. Glinsky, *Hypersensitivity to Streptomycin*, J. Allergy & Clinical Immunology 63, 70 (1951), [https://www.jacionline.org/article/0021-8707\(51\)90131-1/pdf](https://www.jacionline.org/article/0021-8707(51)90131-1/pdf).

⁷⁵ Agrosource FIREWALL 17 WP Fungicide/Bactericide Agricultural Streptomycin, Master Label, Nov. 22, 2015, EPA-HQ-OPP-2016-0067-0017 (“Harmful if absorbed through skin. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Causes moderate eye irritation.”).

Additionally, most farmworkers (53%) have no health insurance,⁷⁶ and limited access to health care, making them particularly vulnerable to environmental and occupational health hazards. Seventy-one percent of workers reported that their employer did not provide health insurance or pay for medical treatment for injuries or illnesses suffered outside of work.⁷⁷ Only 18% of agricultural employers offer health insurance to their workers.⁷⁸

The Agency fails to consider the cumulative effects of take-home exposures or non-occupational spray drift exposures, or dermal exposure with exposures via food, drinking water, and residential use.⁷⁹ These failures lead the EPA to inadequately assess the occupational risk for streptomycin for farmworkers and violates FIFRA, as well as EPA's policies, and its responsibilities under Executive Order 12,898.

EPA has failed to comply with Executive Order 12,898 and in doing so continues to perpetuate environmental injustice for farmworkers, placing them at an unreasonable and disproportionate risk of harm from pesticide use. In the Risk Assessment for streptomycin, the EPA assessed dietary and occupational risks presented by streptomycin independently. Typically, dietary risks are relevant to the general population and occupational risks are primarily related to farmworkers' exposure. Pursuant to Executive Order 12,898, the EPA is obligated to apply equally rigorous methods to the assessment of dietary and occupational risks, as disparate treatment of occupational risk is disparate treatment of the minority and low-income farmworker population. This risk assessment fails to comply with Executive Order 12,898.

In 2009, the EPA adopted a policy titled *Revised Risk Assessment Methods for Workers, Children of Workers in Agricultural Fields, and Pesticides with No Food Uses*, recognizing the need to include aggregate exposure in "risk assessment factors."⁸⁰ According to the EPA, "[t]he principal group that has not been addressed using [these] advanced risk assessment techniques is agricultural workers and their children who may accompany them to work."⁸¹ These farmworkers are frequently migrant workers who are exposed to pesticides from numerous non-occupational sources and may have additional exposure to these same pesticides at their job.⁸² As

⁷⁶ U.S. Dept. of Labor, *Findings from the National Agricultural Workers Survey (NAWS) 2015-2016*, at 41 (Jan. 2018), https://wdr.doleta.gov/research/FullText_Documents/ETAOP_2019-01_NAWS_Research_Report_13.pdf.

⁷⁷ *Id.* at 25

⁷⁸ *Id.* at 25

⁷⁹ This is not even considering the possibility of compounded exposures to other toxic chemicals, fertilizers, and other pesticides that farmworkers can be exposed to in the course of their job or in their housing that is often very near the fields where they work and thus the pesticides sprayed on crops.

⁸⁰ EPA, *Revised Risk Assessment Methods for Workers, Children of Workers in Agricultural Fields and Pesticides with No Food Uses 2* (2009).

⁸¹ *Id.*

⁸² *Id.*

the policy itself points out, failing to extend risk assessment techniques where scientifically justified can have significant environmental justice consequences.⁸³ EPA's continuing failure to consider aggregate exposure in occupational risk assessments continues to subject farmworkers and their families to disproportionate risks to their health and safety.

According to EPA's policy, its "commitment to environmental justice compels it to act expeditiously, where consistent with statutory authority to incorporate the risk assessment techniques developed in the implementation of the [FQPA] in assessing pesticide risks under FIFRA."⁸⁴ By not including aggregate exposure assessments, the Agency fails to honor its commitment to environmental justice. In the nearly 10 years since this policy was adopted, the EPA has failed to uphold it. The EPA's risk assessment for streptomycin is therefore in violation of Executive Order 12,898.

5. The Risk Assessment does not adequately analyze the potential for increased antibiotic resistance from the use of streptomycin on citrus crops, nor does it adequately analyze cumulative potential risks of streptomycin and oxytetracycline.

The emergence of antibiotic resistant bacteria is one of the most significant challenges facing modern medicine today. According to the WHO, the antibiotic resistance crisis requires urgent action and that without great stewardship of antibiotics we are heading for a "post-antibiotic era where common infections and minor injuries can once again kill."⁸⁵ The EPA's proposed decision to increase the pesticidal use of streptomycin, an antibiotic in the medically necessary aminoglycoside family, can only worsen this challenge to modern medicine. Streptomycin has been in use for over 60 years. It is a second line agent in tuberculosis and is efficacious in the treatment of other human diseases, such as brucellosis, tularemia, plague, urinary tract, and endocardial infections.⁸⁶ Contributing to the resistance of bacteria to this vitally important antibiotic threatens public health.

EPA's proposed decision also does not comport with other federal agencies, such as the CDC⁸⁷ and FDA,⁸⁸ policies and positions about preventing antibiotic resistance and promoting antibiotic stewardship. The EPA's Proposed Registration Decision acknowledges that

⁸³ *Id.*

⁸⁴ *Id.* at 3.

⁸⁵ WHO, Antibiotic Resistance Fact Sheet, Feb. 5, 2018, <https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance>.

⁸⁶ Proposed Registration Decision at 11, 12.

⁸⁷ See CDC *supra* n. 23.

⁸⁸ See FDA, Antimicrobial Stewardship, <https://www.fda.gov/EmergencyPreparedness/>

streptomycin resistance does occur in specific bacteria and that with its broader adoption as a control measure for citrus crop, *other resistance may occur*.⁸⁹ Additionally, the Proposed Registration Decision acknowledges that streptomycin resistance in environmental bacteria is documented, but adds that “the effect of transfer of this resistance to bacteria of human health concern is unknown,” and therefore appears to disregard those potential risks.⁹⁰ Further, there have been several reports of foodborne illness from consumption of citrus products involving non-typhoidal serovars of *Salmonella*.⁹¹ This is particularly concerning because there are multiple drug resistant forms of the *Salmonella* microbes of human health concern that could be preferentially selected by any streptomycin residues.⁹² The EPA’s decision to allow the widespread use of streptomycin on citrus crops, while acknowledging it does not know the effect this will have on resistant bacteria, must not stand.

Not only are there potentially life-threatening concerns about antibiotic resistance in bacteria that affect humans, but there is also the real possibility that HLB or citrus canker will become resistant to streptomycin, therefore only increasing the use of streptomycin and thus the exposure risk to farmworkers and consumers.⁹³ The EPA recommends the rotation of streptomycin and oxytetracycline for citrus crops in the hopes that it will prevent resistance; however, EPA’s theory is unsubstantiated by science and in fact, scientific studies demonstrate that rotation does not protect against resistance.⁹⁴

Counterterrorism/MedicalCountermeasures/MCMIssues/ucm620149.htm (last updated Mar. 5, 2019) (“The FDA works closely with domestic and international partners to promote the judicious use of antibiotics in the veterinary setting and complements the work done by other government agencies in the human healthcare setting.”); *see also* FDA, *Supporting Antimicrobial Stewardship in Veterinary Settings Goals for Fiscal Years 2019-2023*, FDA Center for Veterinary Medicine (Sept. 2018), <https://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/UCM620420.pdf>.

⁸⁹ Proposed Registration Decision at 10; *see also* Memo from Samantha Collins & John L. Kough to Fatima Sow, *Review of Antibiotic Resistance Profile of 40 Isolates from CDC’s Repository of Bacterial Isolates for Resistance to Streptomycin or Oxytetracycline*, EPA-HQ-OPP-2016-0067-0012. (“Overall the results of the CDC’s 40 isolate testing confirmed that antibiotic resistance to the plant agricultural antibiotics Streptomycin and Oxytetracycline are found in many clinical bacteria with confirmed multi-drug resistance.”).

⁹⁰ Proposed Registration Decision at 10.

⁹¹ *Id.* at 11 (citations omitted).

⁹² *Id.*

⁹³ *Id.* at 13 (“The likelihood of development of resistance to streptomycin by pathogens causing HLB or citrus canker over time after use of foliar sprays is not known.”).

⁹⁴ *See* Pleun Joppe van Duijn et al., *The Effects of Antibiotic Cycling and Mixing on Antibiotic*

The EPA's Review of Benefits explains that "[t]he likelihood of development of resistance to streptomycin by pathogens causing HLB or citrus canker over time after three foliar sprays per year is not known."⁹⁵ EPA can point to no research, no science, and no data to dispute the very likely potential for increased streptomycin resistant bacteria.

CONCLUSION

For these reasons, EPA's Risk Assessment cannot support the proposed registration decision for streptomycin under FIFRA and does not comply with Agency policy implementing Executive Order 12,898. EPA cannot determine that streptomycin meets the standard for registration because the Agency unreasonably waived all toxicological data requirements, unreasonably removed the FQPA safety factor, failed to adequately assess the risk for farmworkers and their families, as well as consumers, and failed to sufficiently address the potential increase in antibiotic resistant bacteria from widespread use of streptomycin.

We therefore respectfully request EPA deny the registration application for streptomycin or, at the least, revise the Risk Assessment to correct these inadequacies and legal errors and reconsider its conclusions on the basis of the corrected information. Please contact us with any questions.

Sincerely,

Catherine Millas Kaiman, M.P.H.
Florida Bar #117779
Earthjustice
4500 Biscayne Boulevard, Suite 201
Miami, FL 33137
(305) 440-4535
ckaiman@earthjustice.org

Resistance in Intensive Care Units: a Cluster-Randomised Crossover Trial, 18 Lancet Infect. Dis. 401-09 (Jan. 24, 2018), [http://dx.doi.org/10.1016/S1473-3099\(18\)30056-2](http://dx.doi.org/10.1016/S1473-3099(18)30056-2) (in a study of eight randomly selected intensive care units, antibiotic cycling does not reduce the prevalence of carriage of antibiotic-resistant, Gram-negative bacteria in patients admitted to the ICU); Manuel W. Mah & Ziad A. Memish, *Antibiotic Resistance: An Impending Crisis*, 21 Saudi Med. J. 1125, 1127 (2000) (Preliminary studies suggest that "antibiotic cycling policies may speed up the emergence of resistance rather than slow it down."); Marc J. Struelens et al., *Antibiotic Policy: A Tool for Controlling Resistance of Hospital Pathogens*, 5 Clinical Microbiology & Infection, at S22 (Mar. 1999) (Other researchers have found that, at a minimum, the proposed use of "antibiotic rotation" to control resistance "raises more questions than it provides answers regarding the mechanisms of prevention or its practice modalities.")

⁹⁵ Review of Benefits at 9.