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Office of Pesticide Programs Docket
Environmental Protection Agency
Docket Center (EPA/DC) (28221T)
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

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)

The Center for Biological Diversity (Center), Natural Resources Defense Council (NRDC), Sierra Club and U.S. PIRG submit the following comments opposing the Environmental Protection Agency's (EPA) proposed new use registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of the pesticide product streptomycin sulfate for use on citrus crop group 10-10; citrus, dried pulp.

Together, we represent millions of Americans deeply concerned about public health and the environment. The Center is a national, nonprofit organization with more than 1.4 million members and online activists that is dedicated to the protection of rare and imperiled species and the habitats on which they rely. NRDC is a nonprofit environmental and public health advocacy organization headquartered in New York, New York, with more than 3 million members and activists. Among other activities, NRDC engages in research, advocacy, and litigation to improve the regulation of harmful substances in food and consumer products, including drug-resistant bacteria engendered by the misuse and overuse of antibiotics and other antibacterial products. The Sierra Club is working to educate and enlist humanity to protect and restore the quality of the natural and human environment. We believe in the power of people working together to make change happen. As one of the largest and most influential grassroots environmental organization in the U.S., for more than 126 years, we've helped shape the way people can participate in local, state, and national advocacy and policy work, so that we can better explore, enjoy, and protect the planet—and each other. Our 3.5+ million members and supporters have helped in advancing climate solutions and promote the responsible use of the earth's ecosystems and resources. We work alongside other local and national groups because together, we are more powerful. U.S. PIRG, the federation of state Public Interest Research Groups (PIRGs), stands up to powerful special interests on behalf of the American public, working to win concrete results for our health and our well-being. With a strong network of researchers, advocates, organizers and students in state capitals across the country, we take on the special interests on issues such as product safety, public health, campaign finance reform, tax and

budget reform and consumer protection, where these interests stand in the way of reform and progress.

Due to concerns about public health, wildlife safety and the environment, we strongly oppose the proposed expanded use of streptomycin, an antibiotic that is critically important to human medicine and the subject of antibiotic resistance concerns. Streptomycin has been approved for use in certain crops to treat bacterial diseases in plants for decades, however its use has stayed relatively low for many reasons. With the proposed expanded use on citrus, this will undoubtedly change. The sheer amount of diseased citrus acreage in the US, coupled with the high number of proposed treatments per year, makes this proposed use unlike anything the pesticide office has ever grappled with before. Not only will the target bacteria rapidly develop resistance to streptomycin, this resistance can spread to other organisms, threatening human and animal health. Rather than approving new materials to control citrus greening, EPA should take a holistic, comprehensive approach to managing the disease.¹

If finalized in its current form, this approval will greenlight the largest ever use of a medically important antibiotic in plant agriculture in the US. Even compared to the recent approval of oxytetracycline HCL on citrus crops, which is projected to increase by 388,000 pounds per year, streptomycin is still in a league of its own. Due to the higher concentration of streptomycin in available products, current projections indicate that the use of streptomycin just on citrus would likely reach more than 650,000 pounds per year. Add to that the use of streptomycin on other crops and the potential for citrus greening disease to spread further in California and that figure will likely grow over time. Americans use roughly 14,000 pounds of aminoglycosides, the antibiotic class that contains streptomycin, each year to treat disease – nearly 50 times less than what the EPA is proposing to allow on citrus.²

EPA's proposed action here is on a truly unprecedented scale. If it wishes to finalize this proposed decision it must not do so without first:

1. Complying with its duties under Section 7 of the Endangered Species Act (ESA), including completion of consultation;
2. Requiring that the registrant provide all necessary data and studies;
3. Incorporating new analyses into its evaluation and any proposed decision; and
4. Placing appropriate restrictions on uses to avoid and minimize adverse effects.

¹ See, e.g., Ellen F. Cochrane¹ and Jessica B. Shade, Combatting Huanglongbing in Organic Systems, available at <http://aipublications.com/ijhaf/issue-detail/vol-3-issue-1/>. doi: 2 10.22161/ijhaf.3.1.1 (2019).

² Pham T. Drug Use Review. Food and Drug Administration; 2012.

<https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435.pdf>.

DETAILED COMMENTS

I. EPA Should Deny the Application to Register New Uses of Streptomycin Sulfate

All pesticides sold or used in the U.S. must be registered by EPA and based on scientific studies showing that they can be used without posing unreasonable risks or adverse effects to public health or the environment.³ Here, the available evidence indicates that harm to both public health and the environment might occur if this proposed decision is finalized and the new proposed uses of streptomycin approved. It is wholly inappropriate and against sound science for EPA to continue to approve the use of medically important antibiotics such as streptomycin for prophylactic pesticidal purposes, including the control of citrus greening disease. Streptomycin is a member of the aminoglycoside class of antibiotics, a group of human and animal broad-spectrum antibiotics. It is used in the treatment of tuberculosis and other bacterial diseases, such as brucellosis, tularemia, plague, urinary tract and endocardial infections.

In 2003, the Food and Drug Administration (FDA) issued a guidance that included a list of antibiotics that are considered to be important to human medicine.⁴ In that list, FDA separated antibiotics into the following three categories in accordance with their importance in human medicine: critically important (the highest ranking), highly important (the middle ranking), and important (the lowest ranking). The aminoglycoside class – which includes streptomycin – is ranked in that list as being "highly important" to human medicine.⁵ In 2005, the World Health Organization (WHO) developed similar criteria for ranking medically important antibiotics; on the WHO list, aminoglycosides were ranked as "critically important."⁶

Antibiotics such as streptomycin have transformed human and veterinary medicine, making once-lethal infections and diseases readily treatable and curable. Because of the critical importance of these drugs to public health and safety, it has become a national priority to maintain, rather than degrade, the safety and efficacy of these drugs.⁷ In part, that prioritization is the result of the growing antibiotic resistance crisis, both domestically and internationally.⁸

The misuse and abuse of medically important antibiotics is one of the single most important and preventable factors contributing to and accelerating the spread of antibiotic resistance around the

³ 7 U.S.C. § 136a(c)(5); *see also* *Reckitt Benckiser Inc. v. EPA*, 613 F.3d 1131, 1133 (D.C. Cir. 2010).

⁴ Food and Drug Administration, *Evaluating the Safety of Antimicrobial New Animal Drugs with Regards to Their Microbiological Effects on Bacteria of Human Health Concerns*, Guidance for Industry #152 (2003).

⁵ *Id.* at 32.

⁶ World Health Organization, *Critically Important Antimicrobials for Human Medicine*, 5th Revision. Geneva (2016), available at <http://apps.who.int/iris/bitstream/handle/10665/255027/9789241512220-eng.pdf?sequence=1>.

⁷ Exec. Order No. 13,676, Combating Antibiotic-Resistant Bacteria, 79 Fed. Reg. 56,931 (Sept. 18, 2014); *see also* Centers for Disease Control and Prevention, *Antibiotic resistance threats in the United States, 2013* (2013), available at <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>.

⁸ *See, e.g.,* Huttner A, *et al.*, *Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum*, 2(1) *Antimicrobial resistance and infection control* 31(2013).

world.⁹ Bacterial resistance to streptomycin as a result of excess use has long been recognized. “Unlike other medications, the potential for spread of resistant organisms means that the misuse of antibiotics can adversely impact the health of patients who are not even exposed to them. The Centers for Disease Control and Prevention (CDC) estimates more than two million people are infected with antibiotic-resistant organisms, resulting in approximately 23,000 deaths annually.”¹⁰ Some experts contend that the numbers could be much, much higher.¹¹

Due to the gravity of these antibiotic resistance concerns, the president issued an Executive Order (EO) in September 2014 that, among other things, established an interagency Task Force for Combating Antibiotic-Resistant Bacteria, and directed that agencies – including EPA – work together to detect, prevent and control antibiotic resistance through strategic, coordinated and sustained efforts.¹² The specific goals detailed in that EO include:

minimize the emergence of antibiotic-resistant bacteria; *preserve the efficacy of new and existing antibacterial drugs*; advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship; *strengthen surveillance efforts in public health and agriculture*; develop and promote the use of new, rapid diagnostic technologies; accelerate scientific research and facilitate the development of new antibacterial drugs, vaccines, diagnostics, and other novel therapeutics; maximize the dissemination of the most up-to-date information on the appropriate and proper use of antibiotics to the general public and healthcare providers; work with the pharmaceutical industry to include information on the proper use of over-the-counter and prescription antibiotic medications for humans and animals; and *improve international collaboration and capabilities for prevention, surveillance, stewardship, basic research, and drug and diagnostics development*.¹³

In September 2014, the President's Council of Advisors on Science and Technology released a report on antibiotic resistance that recommended strong federal coordination and oversight of efforts to combat antibiotic resistance.¹⁴ Internationally, in January 2014 the WHO recommended that the World Health Assembly (WHA) adopt a resolution on antibiotic resistance that urges countries to take action on the national level to combat the emergence of antibiotic resistant bacteria, and in 2015 the WHA adopted a Global Action Plan on Antimicrobial Resistance.¹⁵ In that

⁹ WHO, Antibiotic Resistance Fact Sheet (2016), available at <http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/> (“Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance.”); Ventola, *The Antibiotic Resistance Crisis; Part 1: Causes and Threats*, 40(4) *Pharmacy & Therapeutics* 277 (2015).

¹⁰ CDC, The Core Elements of Hospital Antibiotic Stewardship Protection, available at <https://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>.

¹¹ Burnham, J., Olsen, M., & Kollef, M. (2019). Re-estimating annual deaths due to multidrug-resistant organism infections. *Infection Control & Hospital Epidemiology*, 40(1), 112-113. doi:10.1017/ice.2018.304.

¹² Exec. Order No. 13,676, Combating Antibiotic-Resistant Bacteria, 79 Fed. Reg. 56,931 (Sept. 18, 2014).

¹³ *Id.* (emphasis added).

¹⁴ Executive Office of the President, President's Council of Advisors on Science and Technology, *Report to the President on Combating Antibiotic Resistance* (2014) (The President's Council was an advisory group comprised of the nation's leading scientists and engineers).

¹⁵ WHO, *Global Action Plan on Antimicrobial Resistance* (2015), available at http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf.

Global Action Plan, the Director of the WHO was clear, "[w]ithout harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill."¹⁶ Despite the change in the administration domestically, the relevance of these efforts continue today.

To date, the focus of national antibiotic stewardship efforts has fallen largely to the healthcare and veterinary health industries. There is no doubt that those efforts are well placed, especially as it relates to the preventable use of antibiotics for growth promotion and other non-therapeutic purposes in animal agriculture, but those efforts should not be pursued to the exclusion of similar stewardship objectives within EPA's pesticide use and approval process. Indeed, stewardship goals should be even more restrictive, and approval conditions narrower, when it comes to pesticidal antibiotic use, which is objectively less critical than the continued efficacy of antibiotics for the treatment of human disease.

In addition to threatening human health and economic security, antibiotic abuse threatens environmental health and safety and endangers exposed wildlife and other creatures. A complete understanding of the ecological effects of antibiotics, their metabolites and degradation products demands more review, but, like all medications, exposure to antibiotics can have serious side effects that include adverse drug reactions, and, as it relates to environmental exposure, changes in the chemical composition and pH of waters, soils and other environmental resources.¹⁷

Antibiotic-resistant bacteria can also spread through contaminated soil and water.¹⁸ Since unintended exposures are common with pesticide use, this proposal signifies a serious potential for adverse effects.

In light of these critical public health and environmental concerns, the agency should deny this application.

¹⁶ *Id.* at i.

¹⁷ See Aga, *et al.*, *Determinations of the Persistence of Tetracycline Antibiotics and their Degradates in Manure-Amended Soil using Enzyme-Linked Immunosorbent Assay and Liquid Chromatography-Mass Spectrometry*, 53 J. Agric. Food Chem. 7165 (2005); Carvalho, *et al.*, *A Review of Plant-Pharmaceutical Interactions: From Uptake and Effects in Crop Plants to Phytoremediation in Constructed Wetlands*, 21 *Envtl Sci. Pollution Res.* 11729 (2014); Cengiz, *et al.*, *Detection of Oxytetracycline and Chlortetracline Residues in Agricultural Fields in Turkey*, 4(10) J. Biol. Envtl. Sci. 23 (2010); Chandler, *et al.*, *Antibacterial Activity of Soil-Bound Antibiotics*, 34(6) J. Envtl. Qual. 1952 (2005); Hamdi, *et al.*, *Gut Microbiome Dysbiosis and Honeybee Health*, 135(7) *Journal of Applied Entomology* 524 (2011); Kay, *et al.*, *Fate of Veterinary Antibiotics in a Macroporous Tile Drained Clay Soil*, 23 *Envtl. Tox. and Chem.* 1136 (2004); Kumar, *et al.*, *Antibiotic Use in Agriculture and its Impact on the Terrestrial Environment*, 87 *Advances in Agronomy* 1 (2005); Raymann, *et al.*, *Antibiotic Exposure Perturbs the Gut Microbiota and Elevates Mortality in Honeybees*, 15(3) *PLoS Biol.* e2001861 (2017); Thiele-Bruhn, *Pharmaceutical Antibiotic Compounds in Soils - A Review*, 166 J. Plant Nutri. Soil Sci. 145 (2003); Wang and Yates, *Laboratory Study of Oxytetracycline Degradation Kinetics in Animal Manure and Soil*, 56 J. Agric. Food Chem. 1683 (2008).

¹⁸ CDC, *Antibiotic Resistance from the Farm to the Table*, available at <https://www.cdc.gov/foodsafety/challenges/from-farm-to-table.html>; Melinda Wenner Moyer, *How Drug-Resistant Bacteria Travel from the Farm to Your Table*, *Scientific American* (Dec. 1, 2016), available at <https://www.scientificamerican.com/article/how-drug-resistant-bacteria-travel-from-the-farm-to-your-table/>; Carvalho, *et al.*, *A Review of Plant-Pharmaceutical Interactions: From Uptake and Effects in Crop Plants to Phytoremediation in Constructed Wetlands*, 21 *Envtl Sci. Pollution Res.* 11729 (2014).

II. EPA Cannot Authorize Any Additional Uses of Streptomycin as Pesticide Before Complying with Its Duties under the Endangered Species Act and FIFRA

EPA must insure that any approved uses of streptomycin as a pesticide do not jeopardize species protected under the ESA or adversely modify or destroy their critical habitat. As a discretionary action that may affect endangered and threatened species, EPA cannot approve this proposed new use without first completing consultation under the ESA with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (the Services).¹⁹ Without such consultation, EPA cannot satisfy its duties under the ESA. Moreover, unless and until EPA completes ESA consultation, any taking of protected species from the use of this pesticide is unlawful.

Specifically, Section 7(a)(2) of the ESA requires that “each federal agency *shall*, in consultation with and with the assistance of the Secretary, insure that any action authorized, funded, or carried out by such agency is not likely to jeopardize the continued existence of any endangered species or threatened species or result in the destruction or adverse modification of habitat of such species which is determined by the Secretary . . . to be critical.”²⁰ The ESA's implementing regulations broadly construe “agency action” to include licensing and permitting actions.²¹

Under the Services’ joint regulations implementing the ESA, EPA is required to review its actions “at the earliest possible time” to determine whether the action may affect listed species or their critical habitat.²² Indeed, in its *Enhancing Stakeholder Input in the Pesticide Registration Review and ESA Consultation Processes* guidance, EPA envisions informal consultations with the Services beginning at the preliminary risk assessment stage.²³ EPA must initiate consultation under Section 7 whenever its action “may affect” a listed species or critical habitat.²⁴ The phrase “may affect” has been interpreted broadly to mean that “any possible effect, whether beneficial, benign, adverse, or of an undetermined character, triggers the formal consultation requirement.”²⁵ Accordingly, due to its continuing and ongoing authority over this pesticide, EPA must consult with the Services to satisfy its duty to insure that any approved use will not jeopardize or adversely modify protected species or their critical habitat, and it must do so *before* it allows any expanded use of this antibiotic-pesticide.

In this instance, to comply with its ESA obligations EPA must consult on the adverse effects of this proposed antibiotic-pesticide, as discussed further in Section I, and all synergistic and cumulative effects of that use. Regarding synergistic and cumulative effects, expanding the range of crops on which this antibiotic is approved for use will likely expand the total amount of

¹⁹ 16 U.S.C. § 1536; *see also* *Washington Toxics Coal. v. EPA*, 413 F.3d 1024, 1033 (9th Cir. 2005).

²⁰ 16 U.S.C. § 1536(a)(2) (emphasis added).

²¹ 50 C.F.R. § 402.02(c).

²² 50 C.F.R. § 402.14(a).

²³ EPA, *Enhancing Stakeholder Input in the Pesticide Registration Review and ESA Consultation Process and Development of Economically and Technologically Feasible Reasonable and Prudent Alternatives*, at 7 (Mar. 19, 2013), *available at* Docket ID EPA-HQ-OPP-2012-0442.

²⁴ 50 C.F.R. § 402.14(a).

²⁵ *Western Watersheds Project v. Kraayenbrink*, 632 F.3d 472, 496 (9th Cir. 2011) (finding that the threshold for triggering ESA consultation “is relatively low”) (quoting 51 Fed. Reg. at 19,949); *Lockyer v. U.S. Dep’t of Agric.*, 575 F.3d 999, 1018 (9th Cir. 2009).

antibiotic-pesticides being used in any given period of time. Since streptomycin may be applied to the same crop types with other pesticides, like copper and oxytetracycline, its approval and increased application may result in synergistic effects.

If the Services conclude that "the agency action would place the listed species in jeopardy or adversely modify its critical habitat," then it must provide "reasonable and prudent alternatives" to the proposed action.²⁶

At a minimum, where a product may affect listed species, all product labels must contain the following language:

This product may have effects on federally listed threatened or endangered species or their critical habitat in some locations. When using this product, you must follow the measures contained in the Endangered Species Protection Bulletin for the county or parish in which you are applying the pesticide. To determine whether your county or parish has a Bulletin, and to obtain that Bulletin, consult <http://www.epa.gov/espp/>, or call 1-800-447-3813 no more than 6 months before using this product. Applicators must use Bulletins that are in effect in the month in which the pesticide will be applied. New Bulletins will generally be available from the above sources 6 months prior to their effective dates.²⁷

See Appendix A for more on EPA's requirements under the ESA.

III. EPA Must Require that the Registrant Provide All Necessary Data and Studies

The agency must require all necessary data and studies, including, but not limited to, any previously identified data gaps; additional studies to evaluate effects on imperiled species, including on pollinators in accordance with the *Guidance for Assessing Pesticide Risks to Bees*²⁸; information concerning antibiotic resistance and estrogen or other endocrine disruption effects²⁹; and any information that products containing this antibiotic-pesticide may have synergistic effects or have synergistic effects with other pesticides or environmental stressors.

The current ecological risk assessment for this proposed new use of streptomycin on citrus acknowledges a deficiency in pollinator toxicity data.³⁰ In fact, the Tier 1 requirements (the bare minimum of studies required under EPA guidance under FIFRA) are not even met, with only an acute contact toxicity study having been performed for streptomycin. This is completely

²⁶ *Nat'l Ass'n of Home Builders v. Defs. of Wildlife*, 551 U.S. 644, 652 (2007) (citing 16 U.S.C. § 1536(b)(3)(A); see also 50 C.F.R. § 402.14(h)(3).

²⁷ *Endangered Species Protection Program Field Implementation*, 70 Fed. Reg. 66392 (Nov. 2, 2005).

²⁸ EPA, *Guidance for Assessing Pesticide Risks to Bees* (2014), available at https://www.epa.gov/sites/production/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf;

²⁹ See 21 U.S.C. §§ 346a(d)(2)(A)(x), 346a(p).

³⁰ Shelby, A, Section 3 Proposed New Use of Streptomycin Sulfate on Citrus, Crop Group 10-10 [Memorandum] (Nov. 20, 2017), available at Docket ID EPA-HQ-OPP-2016-0067-0006.

inadequate, not only in light of the harms demonstrated in published, peer-reviewed studies (as discussed below), but also with the agency's new guidelines for pollinator risk assessment.³¹

Adult worker bees that were treated with an antibiotic mixture containing streptomycin had negative impacts to their immune systems and, after being inoculated with the *Nosema ceranae* parasite, had significantly higher *Nosema* levels than inoculated bees that were not treated with the antibiotic.³² Microcolonies of bumblebees treated with an antibiotic mixture containing streptomycin or streptomycin alone experienced changes in their gut bacterial community that resulted in changes in the fitness of the bees in the colony.³³ *Enterobacteriaceae spp* in bee bread from 15 different colonies were found to be susceptible to streptomycin, indicating this antibiotic could affect microbial communities within the hive.³⁴ Streptomycin in the bee diet decreased the numbers of intestinal bacteria and increased the number of intestinal yeasts in the bees.^{35,36} Honeybees foraging in environments that had high streptomycin exposure had gut bacteria with significantly higher prevalence of streptomycin resistance than that of bees that had lower exposure.³⁷ This indicates that streptomycin can impact the microbial gut communities of bees and this can lead to immune system impacts and greater susceptibility to pathogen infection.

These studies support the hypothesis that streptomycin can negatively affect the microbial communities in honey and bumble bees and this can increase the severity of pathogen infection. This hypothesis is further supported by the demonstrated effects of many different antibiotics on bee gut flora and the known effects to the immune system due to changes in the gut microbiome.³⁸ It is the duty of EPA to determine whether peak residues that will be encountered

³¹ EPA, *Guidance for Assessing Pesticide Risks to Bees* (2014), available at https://www.epa.gov/sites/production/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf;

³² Li, J. H., Evans, J. D., Li, W. F., Zhao, Y. Z., DeGrandi-Hoffman, G., Huang, S. K., Chen, Y. P., New evidence showing that the destruction of gut bacteria by antibiotic treatment could increase the honey bee's vulnerability to *Nosema* infection, *PLOS ONE*, 12(11), e0187505. doi:10.1371/journal.pone.0187505 (2017).

³³ Meeus, I., Mommaerts, V., Billiet, A., Mosallanejad, H., Van de Wiele, T., Wäckers, F., & Smagghe, G., Assessment of mutualism between *Bombus terrestris* and its microbiota by use of microcolonies, *Apidologie*, 44(6), 708-719. doi:10.1007/s13592-013-0222-9 (2013).

³⁴ Randolph, C.E, *Bacteria Involved in the Health of Honey Bee (Apis Mellifera) Colonies* (Master's thesis), University of Delaware (2014), available at

http://udspace.udel.edu/bitstream/handle/19716/16908/2014_RandolphClinita_MS.pdf?sequence=1&isAllowed=y.

³⁵ Gilliam M. Lorenz B.J. Richardson G.V., Digestive enzymes and micro-organisms in honey bees, *Apis mellifera*: influence of streptomycin, age, season and pollen, *Microbios* 55, 95-114 (1988).

³⁶ Gilliam, M., Identification and roles of non-pathogenic microflora associated with honey bees, *FEMS Microbiology Letters*, 155(1), 1-10. doi:10.1016/s0378-1097(97)00337-6 (1997).

³⁷ Ludvigsen, J., Amdam, G. V., Rudi, K., & L'Abée-Lund, T. M., 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*, 76(3), 588-591. doi:10.1007/s00248-018-1171-7 (2018).

³⁸ Tian, B., Fadhil, N. H., Powell, J. E., Kwong, W. K., & Moran, N. A., Long-Term Exposure to Antibiotics Has Caused Accumulation of Resistance Determinants in the Gut Microbiota of Honeybees, *mBio*, 3(6), doi:10.1128/mbio.00377-12 (2012); Raymann, K., Shaffer, Z., & Moran, N. A., Antibiotic exposure perturbs the gut microbiota and elevates mortality in honeybees, *PLOS Biology*, 15(3), e2001861, doi:10.1371/journal.pbio.2001861 (2017); Raymann, K., & Moran, N. A., The role of the gut microbiome in health and disease of adult honey bee workers, *Current Opinion in Insect Science*, 26, 97-104, doi:10.1016/j.cois.2018.02.012 (2018); Blaser, M. J., Antibiotic use and its consequences for the normal microbiome, *Science*, 352(6285), 544-545. doi:10.1126/science.aad9358 (2016); Raymann, K., Bobay, L., & Moran, N. A., Antibiotics reduce genetic diversity

in the environment after spraying could decrease the fitness of pollinators and other terrestrial insects via effects on the gut microbiome. This should be a science-based analysis—conjecture is not sufficient.

While the whole suite of Tier 1 pollinator studies will be needed before EPA can make a decision to expand the use of streptomycin, these alone will not be sufficient. EPA's typical guideline studies are not designed to identify the effects demonstrated in the published literature. EPA will not only need to require studies that look at the microbiome as an endpoint, but also look at differing effects on bees that have been stressed with an infection. Managed honeybees and native bees are not always healthy and are under constant attack by pathogens. Any impact to the immune system of these important animals must be analyzed in the context of this approval. Studies done solely on unstressed bee populations will not be sufficient.

Citrus trees are some of the most highly attractive agricultural crops for bees to collect pollen and nectar.³⁹ Citrus flowers are renowned magnets for bees. As per the proposed pesticide label, the first treatment of streptomycin will be made during the spring flush and thereafter⁴⁰ – the exact same time the citrus tree is flowering. Therefore, not only are citrus flowers highly attractive to bees, but the trees will be treated while the flowers are in bloom. The potential for exposure to pollen and nectar containing a known immunosuppressant is extremely high and this will likely have significant impacts on pollinator health and significant economic impacts due to lower crop pollination in Florida and California. If EPA finalizes this proposed decision without further analysis into the potential impacts to bees and other pollinators, the agency will be in violation of its duties under FIFRA.

IV. EPA Must Revise Its Analysis of the Potential for Antibiotic Resistance to Develop

While EPA recognizes the potential implications that this proposed decision will have on antibiotic resistance, the agency does not fully outline the risks involved. The analysis of streptomycin safety under FDA guidance #152 was insufficient and was not properly used in EPA's proposed decision.

EPA acknowledges that “[b]ased on current use data, there are 36,000 lbs of streptomycin used on approximately 365,000 acres of apples and pears. The expansion would represent 480,000 acres of remaining Florida citrus production (NASS, 2017) at 1.36 lbs streptomycin annually or

of core species in the honeybee gut microbiome, *Molecular Ecology*, 27(8), 2057-2066. doi:10.1111/mec.14434 (2017); Ludvigsen, J., Porcellato, D., L'Abée-Lund, T. M., Amdam, G. V., & Rudi, K., Geographically widespread honeybee-gut symbiont subgroups show locally distinct antibiotic-resistant patterns, *Molecular Ecology*, 26(23), 6590-6607. doi:10.1111/mec.14392 (2017).

³⁹ USDA, Attractiveness of Agricultural Crops to Pollinating Bees for the Collection of Nectar and/or Pollen (2017), available at https://www.ars.usda.gov/ARSUserFiles/OPMP/Attractiveness%20of%20Agriculture%20Crops%20to%20Pollinating%20Bees%20Report-FINAL_Web%20Version_Jan%203_2018.pdf.

⁴⁰ Agrosource. FIREWALL™ 17 WP Fungicide/Bactericide Agricultural Streptomycin label, available at Docket ID EPA-HQ-OPP-2016-0067-0017.

652,800 lbs. This represents an 18-fold increase in the current use amount.”⁴¹ Therefore, the increase in use of streptomycin will be significant and widespread.

Published research indicates that streptomycin resistance has already developed in species of bacteria similar to that which cause citrus canker, indicating that it is only a matter of time before this antibiotic is ineffective against this disease.^{42,43} The traits in these bacteria are also similar to those found in some human health pathogens, further highlighting the ease with which these traits can transfer from bacteria that are not of human health concern to those that are.⁴⁴ In addition, contaminated citrus fruits have caused food-related illnesses in previous instances, particularly with *Salmonella*.⁴⁵ Therefore, citrus provides a pathway by which humans can be exposed to human health pathogens; and if resistance traits develop in bacteria in citrus fields, this could be a significant source of exposure to streptomycin-resistant pathogens.

Furthermore, FDA’s #152 analysis does not discuss the potential spread of streptomycin-resistant bacteria or plasmids via insect vectors.⁴⁶ Recent research indicates that bees that forage in areas where streptomycin exposure is high have a higher prevalence of gut bacteria that contain streptomycin resistance genes on transferrable plasmids.⁴⁷ Identical transposons were also identified in the human health pathogen, *E.coli*.⁴⁸ Therefore, bees can pick up streptomycin resistance genes either from being exposed to streptomycin-resistant bacteria on citrus blooms or having their own gut bacteria develop resistance after chronic, low-level exposure.

Streptomycin-resistant bacteria and genes can then be transported miles away from treated fields.

Therefore, EPA should rate this proposed streptomycin use as being “high” risk for the development of antibiotic resistance based on the unprecedented magnitude of proposed use in plant agriculture, the similarity of streptomycin resistant traits in *Xanthomonas spp.* and those in

⁴¹ Collins, S. Review of AgroSource’s Analysis of Streptomycin’s Safety with Regard to Its Microbiological Effect on Bacteria of Human Health Concern (FDA/CVM Guidance to Industry #152) for a Section 3 Registration on Citrus Crop Group 10-10, at 7 (Oct. 25, 2017), *available at* Docket ID EPA-HQ-OPP-2016-0067-0015.

⁴² Yong Zhang, A study on the mechanism of resistance to streptomycin in *Xanthomonas oryzae* pv. *Oryzae*, *AFRICAN JOURNAL OF BIOTECHNOLOGY*, 10(79). doi:10.5897/ajb11.628 (2011).

⁴³ Minsavage GV, Plasmid-Mediated Resistance to Streptomycin in *Xanthomonas campestris* pv. *vesicatoria*. *Phytopathology*, 80:719 (1990).

⁴⁴ Sundin GW, Bender CL, Expression of the strA-strB streptomycin resistance genes in *Pseudomonas syringae* and *Xanthomonas campestris* and characterization of IS6100 in *X. campestris*. *Appl Environ Microbiol.* 1995;61:2891–7.

⁴⁵ Collins, S., Review of AgroSource’s Analysis of Streptomycin’s Safety with Regard to Its Microbiological Effect on Bacteria of Human Health Concern (FDA/CVM Guidance to Industry #152) for a Section 3 Registration on Citrus Crop Group 10-10, at 7 (Oct. 25, 2017), *available at* Docket ID EPA-HQ-OPP-2016-0067-0015.

⁴⁶ *Id.*

⁴⁷ Ludvigsen, J., Amdam, G. V., Rudi, K., & L’Abée-Lund, T. M., 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*, 76(3), 588-591. doi:10.1007/s00248-018-1171-7 (2018).

⁴⁸ *Id.*

human pathogens, reported food-borne illnesses from citrus fruits, and the potential for animal vectors to spread antibiotic-resistant bacteria or plasmids.

If EPA decides to retain its “medium” risk rating, then it must do more to lower the potential use of this product. As the proposed approval stands, this would be considered a very high use of an antibiotic. Table 8 in FDA guidance #152 does not even have an option for the approval of an antibiotic with “medium” risk that has a high extent of use, indicating this is a highly unusual occurrence.⁴⁹ Furthermore, most “medium” risk approvals require a prescription from a veterinarian. Oversight from a veterinarian is not relevant in plant agriculture, but there is precedence for having a professional involved in the use of an antibiotic with this risk profile. Making streptomycin a restricted use pesticide (RUP) would ensure that people who were not professionals did not use this product. Right now there is only a non-enforceable recommendation that streptomycin is used only by professionals.⁵⁰ This “recommendation” is meaningless and, as it stands now, anyone will be able to purchase streptomycin on the internet and use it at their residence or farming operation. That is dangerous and undermines other steps that have been taken to reduce the potential for misuse of this product.

V. EPA Must Place Appropriate Restrictions on Use to Avoid and Minimize Adverse Effects

EPA has broad authority to restrict uses and place strong mitigation language on labels for new uses. Due to the inherently risky nature of approving a medically important antibiotic for widespread use as a pesticide, both generally and specifically as it relates to this application, EPA must use its authority to place appropriately restrictive limitations on this use to avoid and minimize adverse effects. In its proposed decision, the agency has not done this.

For a determination of ecological risk, EPA analyzed the potential for plants and animals to be harmed by the proposed decision. By comparing the potential for exposure and toxicity from streptomycin, the agency identified whether streptomycin encountered in treated fields would result in harm. Despite having levels of concern exceeded for mammals by nearly 10-fold and non-vascular plants by more than 3-fold, EPA did not require any measures whatsoever to prevent or mitigate the identified harm to these taxa.⁵¹

EPA’s proposed Resistance Management Plan (RPM) is completely inadequate and will not be effective. The resistance management plan consists of 1) stating the mechanism of action of the pesticide label, 2) stating the application dose on the label, 3) voluntary recommendation that the

⁴⁹ FDA, # 152 Guidance for Industry, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern (2003), *available at* <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf>.

⁵⁰ Agrosource, FIREWALL™ 17 WP Fungicide/Bactericide Agricultural Streptomycin label, available at Docket ID EPA-HQ-OPP-2016-0067-0017.

⁵¹ EPA, Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10 (Dec. 21, 2018), *available at* Docket ID EPA-HQ-OPP-2016-0067-0023.

field should be scouted for lack of performance, 4) voluntary recommendation that lack of performance should be reported to the company, 5) label statement outlining voluntary measures that can be taken to prevent resistance, 6) label statements on local resistant pests, 7) requirement that the registrant report lack of performance to EPA, 8) educational materials be provided to growers.⁵² Therefore, the RPM consists of making factual statements on the pesticide label and voluntary measures that are not sufficient to avoid and minimize adverse effects. The only mandatory requirement is that Agrosource report lack of performance to EPA, but all of this depends on growers voluntarily reporting lack of performance issues to Agrosource.

The entire RPM is predicated and dependent on thousands upon thousands of individual farmers and farmworkers doing something that is time consuming and is not required of them. Such a model is designed to fail.

Furthermore, EPA has required annual monitoring of antibiotic resistance from the registrant, but fails to provide any details on how this monitoring will be performed, what bacterial strains will be analyzed, what resistance genes will be analyzed, and how potential antibiotic resistance in human pathogens can be traced back to citrus groves.⁵³ These are incredibly complex experiments with the potential for erroneous interpretation and poor study design. Allowing the registrant to develop experiments and protocols to submit to the agency is inadequate and must be subject to oversight by experts at CDC and FDA and open for public notice and comment. EPA simply does not have enough expertise in the area of antibiotic resistance to provide sufficient oversight of these studies.

VI. EPA Should Incorporate Input from Its Federal Partners

It appears as though EPA has decided to ignore the FDA and CDC in its proposed approval of streptomycin on citrus. EPA states: “Our federal partners expressed a number of concerns on expanding uses of antibiotics in plant agriculture. *Overall, they recommend judicious use, prevention of drift to neighboring fields/water bodies, and additional protection of agricultural pesticide handlers from exposure.*”⁵⁴

EPA has not, however, imposed any meaningful use restrictions to ensure judicious use. As it stands now, streptomycin will be able to be used on any citrus tree anywhere in the U.S. Even though streptomycin *has not been shown* to prevent transmission of citrus greening disease, the label allows it to be used as a preventative measure (“[u]se only to treat/prevent proven bacterial infections”⁵⁵). Therefore, the tree does not even have to be infected to be treated with streptomycin. **There is nothing less judicious than using an antibiotic as a preventative**

⁵² Chandgoyal, T., Review of Label Language and Resistance Management Plan for Streptomycin Sulfate on Citrus Crop Group 10- 10 (PC# 006310 and DP # 440091 ; M RID 50281703) [Memorandum] (Nov 28, 2017), *available at* Docket ID EPA-HQ-OPP-2016-0067-0011.

⁵³ EPA, Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10 (Dec. 21, 2018), *available at* Docket ID EPA-HQ-OPP-2016-0067-0023.

⁵⁴ *Id.* at 17 (emphasis added).

⁵⁵ *Id.* at 17.

measure when it has not even been shown to successfully prevent the spread of disease.

Without any scientific support for streptomycin being a proven preventative agent, any label language alluding to this must be removed. The label should state that this product should not be used to prevent disease spread.

Furthermore, no measures have been taken to prevent drift to neighboring fields/water bodies. The agency prohibits aerial spraying, which was not even requested in the original application and is not a commonly used pesticide treatment strategy in citrus groves. Additionally, aerial application was already prohibited by the label even before the new citrus use was proposed. The agency, instead, has allowed the second most drift-prone dissemination method of a pesticide: airblast. Airblast consists of putting huge industrial fans on the back of a truck and having the fans blow out ultrafine liquid droplets of the pesticide onto trees. It is incredibly imprecise and results in an enormous amount of drift off of the treated field. The label for streptomycin does not even have a wind speed cutoff, thereby allowing this antibiotic to be sprayed by airblast in very windy conditions.⁵⁶

This allowance is even more glaringly lax because a more prudent approach of treating trees for citrus greening disease is available. For example, tree trunk injection with streptomycin has been shown to be more effective at combating citrus greening disease than foliar spraying and results in less drift, better treatment of bacteria in the tree's phloem, less runoff and much less exposure to off-target organisms.⁵⁷ The possibility of this better alternative was not, however, even discussed.

The agency's PPE requirements are similar to the minimum required for nearly all agricultural pesticides: basically, clothes and gloves. The agency has added the protection of a respirator requirement and neck covering. However, this is not proposed to be a restricted use pesticide (RUP) and the label language, "[i]ntended for use by professional applicators," is guidance only. Without a reasonable expectation that non-professionals won't use the product, the potential for misuse is high.

Therefore, despite input from CDC and FDA, EPA has ignored their expertise and has opted to move forward without common sense protections. EPA's proposed approval will not result in judicious use, drift mitigation or protections for non-professionals using the product.

VII. EPA Must Analyze how Real-world Use Can Increase the Severity of Antibiotic Resistance

EPA attempts to downplay the potential for antibiotic resistance to spread by saying that antibiotics with different mechanisms of action (streptomycin and oxytetracycline) will be cycled

⁵⁶ Agrosource, FIREWALL™ 17 WP Fungicide/Bactericide Agricultural Streptomycin label, *available at* Docket ID EPA-HQ-OPP-2016-0067-0017.

⁵⁷ Hu, J., Jiang, J., & Wang, N., Control of Citrus Huanglongbing via Trunk Injection of Plant Defense Activators and Antibiotics, *Phytopathology*, 108(2), 186-195. doi:10.1094/phyto-05-17-0175-r (2018).

in treating trees infected by citrus greening disease. Further, streptomycin will likely be used in conjunction, or in cycle, with copper to treat citrus canker.

EPA makes the claim that cycling between drugs with two different mechanisms of action will prevent or delay resistance from occurring. This is not backed up with any data. In fact, antibiotic cycling is not used in a clinical setting because it has been shown to have no effect on the development or prevalence of resistant bacteria.^{58,59}

Thus, there is no indication that cycling antibiotics will prevent or delay resistance; however, there is a risk that multiple drug resistance will develop under such a strategy. EPA states that “[m]ultiple drug resistance is carried on single plasmids in many bacteria of human health concern and oxytetracycline/streptomycin resistance is a common trait on these plasmids.”⁶⁰ This is worrisome because multiple drug resistance to these two antibiotics has already occurred and is characterized in human health pathogens. Cycling between these two antibiotics will increase the likelihood that multiple drug resistance will develop out in the field and these traits can be transferred between strains on these single plasmids.

Further, copper will likely be used in conjunction with streptomycin to treat citrus canker. Large plasmids that contain copper resistance have been shown to transfer between species of bacteria.⁶¹ Copper is currently used to coat surfaces in hospitals to lower the microbial burden on contaminated surfaces.⁶² Copper is, therefore, widely used by hospitals as a way to combat disease spread. The potential for multiple drug resistance to develop (i.e. resistance to both copper and streptomycin on a single plasmid) will reduce the ability of both these drugs to prevent or treat human disease. The known ability of metals to impose a selection pressure on bacteria and, perhaps, facilitate antibiotic resistance makes this a worrisome prospect.⁶³

Antibiotic cycling should, therefore, not be used as a way to dismiss concerns about antibiotic resistance developing (as EPA has currently done in the proposed decision). Rather, it should be analyzed for what it is: a cause for greater concern about the potential human health and economic implications behind this decision.

⁵⁸ Kollef, M. H., Is Antibiotic Cycling the Answer to Preventing the Emergence of Bacterial Resistance in the Intensive Care Unit? *Clinical Infectious Diseases*, 43(Supplement_2), S82-S88, doi:10.1086/504484 (2006).

⁵⁹ Van Duijn, P. J., Verbrugghe, W., Jorens, P. G., Spöhr, F., Schedler, D., Deja, M., Roca, I., The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: a cluster-randomised crossover trial, *The Lancet Infectious Diseases*, 18(4), 401-409. doi:10.1016/s1473-3099(18)30056-2 (2018).

⁶⁰ Collins, S., Review of AgroSource’s Analysis of Streptomycin’s Safety with Regard to Its Microbiological Effect on Bacteria of Human Health Concern (FDA/CVM Guidance to Industry #152) for a Section 3 Registration on Citrus Crop Group 10-10, at 6 (Oct. 25, 2017), available at Docket ID EPA-HQ-OPP-2016-0067-0015.

⁶¹ Behlau, F., Canteros, B. I., Jones, J. B., & Graham, J. H., Copper resistance genes from different xanthomonads and citrus epiphytic bacteria confer resistance to *Xanthomonas citri* subsp. *Citri*, *European Journal of Plant Pathology*, 133(4), 949-963, doi:10.1007/s10658-012-9966-8 (2012).

⁶² Schmidt, M. G., Attaway, H. H., Sharpe, P. A., John, J., Sepkowitz, K. A., Morgan, A., Salgado, C. D., Sustained Reduction of Microbial Burden on Common Hospital Surfaces through Introduction of Copper, *Journal of Clinical Microbiology*, 50(7), 2217-2223, doi:10.1128/jcm.01032-12 (2012).

⁶³ Baker-Austin, C., Wright, M. S., Stepanauskas, R., & McArthur, J., Co-selection of antibiotic and metal resistance, *Trends in Microbiology*, 14(4), 176-182, doi:10.1016/j.tim.2006.02.006 (2006).

VIII. EPA's Assessment of Streptomycin Use on Citrus Is Flawed and Overstates the Benefits This Antibiotic Would Provide

This proposed approval relies on an inadequate and flawed risk-benefit analysis. The risks are clear: there will likely be harm to mammals, non-vascular plants and pollinators. There is also a significant risk of antibiotic resistance developing, which includes the development of multiple drug resistance (to streptomycin, copper and oxytetracycline).

EPA concluded that this new use would benefit citrus growers because there is modest efficacy against the bacteria that causes citrus greening disease.⁶⁴ Yet, the approval is much broader, covering preventive uses.

But, streptomycin is not recognized as being effective in preventing the spread of citrus greening disease. Currently the only known way to prevent the movement of citrus greening disease is to remove and destroy infected trees early in the disease-cycle. That is the only method that is known to work. The problem with any chronic, long-term treatment – like the one proposed with streptomycin – is that trees that should be removed will now be spared and put in long-term treatment. While no one wants to see these diseased trees perish, their presence is perpetuating the spread of this disease to uninfected plants.

Since streptomycin is not effective at preventing the spread of the disease, by approving this new use EPA could actually be perpetuating the spread of this disease because trees that would have been removed in an effective prevention strategy would now remain in place. EPA failed to discuss this possibility and to analyze the consequent potential for further spread of this disease – particularly in California where effective prevention strategies are extremely important right now – as a risk factor in perpetuating disease spread.

It's important to recognize that this proposed approval will not result in replacement of current pesticide use strategies and it will not result in decreased pesticide use. EPA's review of the benefits assessment states: "This approach would be supplemented with other measures including continued insecticidal programs for ACP control...",⁶⁵ indicating that insecticide control of the Asian citrus psyllid will not be affected by this proposed new use approval. Therefore, the chemical load in the environment will undeniably increase. This was not discussed and explored in EPA's cost-benefit analysis.

EPA states: "BEAD concurs that, generally, resistance management strategies that include alternating two or more different modes of action would be considered a benefit for reducing the likelihood of plant pathogen developing resistance to an individual pesticide."⁶⁶ As outlined above, many in the public health community would disagree with this statement as there is no

⁶⁴ Chandgoyal, T., Review of Benefits of a New Use of Streptomycin Sulfate (Fire Wall™ SOWP) on of Citrus Crop Group 10-10 (PC# 006310 ; DP# 440664; MRID# 50281701) [Memorandum] (Nov. 22, 2017), *available at* Docket ID EPA-HQ-OPP-2016-0067-0010.

⁶⁵ *Id.* at 4.

⁶⁶ *Id.* at 5.

consensus that antibiotic mixing or cycling prevents or impacts the prevalence of antibiotic resistant bacteria.^{67,68} Furthermore, the idea of this being a “benefit” is quite a stretch, as it is only beneficial in light of EPA’s flawed recent approval of oxytetracycline on citrus. Two wrongs don’t make a right and EPA can’t suddenly say that this streptomycin approval is beneficial because it’s needed to reduce the risks from EPA’s prior approval of oxytetracycline.

EPA’s entire benefits assessment rests on “the almost non-existent strategies” that are currently approved to control citrus greening disease as the sole justification for its proposed approval.⁶⁹ However, the benefits are so modest as to be almost indistinguishable from those that could arise from chance alone. Many of the proposed benefits were measured with a statistical significance cutoff of $p < 0.1$.⁷⁰ This is highly unconventional and no scientific body or journal in the world recognizes this as an appropriate cutoff to determine whether effects are treatment-related or due to chance. This is particularly troublesome with the fact that all of the toxicity studies EPA analyzed for the harms from streptomycin used the conventional significance cutoff of $p < 0.05$. EPA is, therefore, using a statistical threshold that is more stringent when analyzing the harms from streptomycin and less stringent when analyzing the supposed benefits of streptomycin. This is absolutely unacceptable and biases towards the benefits of this action in the cost-benefit analysis.

Furthermore, the benefits assessment for citrus canker was not conducted correctly. The benefits of streptomycin were only analyzed in conjunction with copper. There was no “copper alone” treatment in this study, therefore any benefit associated with the streptomycin + copper treatment cannot be attributed to streptomycin. The interpretation of the results is highly flawed and EPA cannot conclude that streptomycin had any effect on the outcomes in that experiment.⁷¹

All of the above-mentioned shortcomings in the benefits assessment are in addition to published research indicating that streptomycin is not effective at treating citrus greening disease.⁷² Therefore, EPA’s benefits analysis is flawed, overstates the benefits of the proposed decision, does not demonstrate that the benefits of the proposed decision outweigh the risks, and omits important information about lack of efficacy of streptomycin.

⁶⁷ Kollef, M. H., Is Antibiotic Cycling the Answer to Preventing the Emergence of Bacterial Resistance in the Intensive Care Unit? *Clinical Infectious Diseases*, 43(Supplement_2), S82-S88, doi:10.1086/504484 (2006).

⁶⁸ Van Duijn, P. J., Verbrugge, W., Jorens, P. G., Spöhr, F., Schedler, D., Deja, M., Roca, I., The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: a cluster-randomised crossover trial, *The Lancet Infectious Diseases*, 18(4), 401-409. doi:10.1016/s1473-3099(18)30056-2 (2018).

⁶⁹ Chandgoyal, T. Review of Benefits of a New Use of Streptomycin Sulfate (Fire Wall™ SOWP) on of Citrus Crop Group 10-10 (PC# 006310 ; DP# 440664; MRID# 50281701) [Memorandum], at 5 (Nov. 22, 2017), available at Docket ID EPA-HQ-OPP-2016-0067-0010.

⁷⁰ *Id.* at 5, 8.

⁷¹ *Id.* at 8.

⁷² Zhang, M., Guo, Y., Powell, C. A., Doud, M. S., Yang, C., & Duan, Y., Effective Antibiotics against ‘Candidatus Liberibacter asiaticus’ in HLB-Affected Citrus Plants Identified via the Graft-Based Evaluation, *PLoS ONE*, 9(11), e111032, doi:10.1371/journal.pone.0111032 (2014).

CONCLUSION

This proposed decision will greenlight the largest ever use of a medically important antibiotic in plant agriculture in the U.S. The stakes are very high and the analysis that EPA conducted is inadequate. Due to the risks outlined in these comments and the overstated benefits of this new streptomycin use, EPA should deny this new use application. FIFRA and the ESA are clear on what EPA must do when harms of this nature are evident and this proposed decision does not satisfy EPA's duties under these two statutes.

If EPA were to deny this application it would be in alignment with its peer agencies in Brazil and the European Union, both of which have banned the use of streptomycin in plant agriculture.^{73,74} While citrus greening poses an urgent threat, moving forward with this proposed decision would be worse than doing nothing. Even in the best-case scenario, the modest potential benefits of this use are not worth the high risks. And the best-case scenario does not comport with the evidence, which shows that use of streptomycin is not effective for the purposes that EPA proposes to approve. EPA should deny this application.

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⁷³ Agência Nacional De Vigilância Sanitária (ANVISA). Regularização de Produtos - Agrotóxicos. Monografias Excluídas. <http://portal.anvisa.gov.br/registros-e-autorizacoes/agrotoxicos/produtos/monografia-de-agrotoxicos/excluidas>.

⁷⁴ European Commission. EU Pesticides database. Search active substances. <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN>.

Appendix A

ENDANGERED SPECIES ACT CONSULTATION OBLIGATIONS FOR PESTICIDE APPROVALS BY THE ENVIRONMENTAL PROTECTION AGENCY

I. EPA Has an Independent Duty Under the Endangered Species Act to Consult with the U.S. Fish and Wildlife Service and National Marine Fisheries Service on Pesticide Approvals.

Section 7(a)(2) of the ESA requires that “each federal agency *shall*, in consultation with and with the assistance of the Secretary, insure that any action authorized, funded, or carried out by such agency is not likely to jeopardize the continued existence of any endangered species or threatened species or result in the destruction or adverse modification of habitat of such species which is determined by the Secretary... to be critical.”⁷⁵ Under Section 7(a)(2), EPA must consult with the U.S. Fish and Wildlife Service and National Marine Fisheries Service (collectively the “Services”) to determine whether its actions will jeopardize listed species’ survival or adversely modify designated critical habitat, and if so, to identify ways to modify the action to avoid that result.⁷⁶ The consultation requirement applies to any discretionary agency action that may affect listed species.⁷⁷ Because EPA may decline to approve pesticides and uses, its decision represents a discretionary action that clearly falls within the ESA’s consultation requirement.⁷⁸

EPA must initiate consultation under Section 7 whenever its action “may affect” a listed species or critical habitat.⁷⁹ Under the Services’ joint regulations implementing the ESA, EPA is required to review its actions “at the earliest possible time” to determine whether the action may affect listed species or critical habitat.⁸⁰ Indeed, EPA’s policy *Enhancing Stakeholder Input in the Pesticide Registration Review and ESA Consultation Processes* envisions informal consultations with the Services beginning at the preliminary risk assessment stage.⁸¹ The Services define “may affect” as “the appropriate conclusion when a proposed action may pose

⁷⁵ 16 U.S.C. § 1536(a)(2) (emphasis added).

⁷⁶ 50 C.F.R. § 402.14.

⁷⁷ *National Association of Home Builders v. Defenders of Wildlife*, 551 U.S. 644 (2007).

⁷⁸ See *Washington Toxics Coalition v. EPA*, 413 F. 3d 1024, 1032 (9th Cir. 2005) (“even though EPA registers pesticides under FIFRA, it must also comply with the ESA when threatened or endangered species are affected.”).

⁷⁹ 50 C.F.R. § 402.14(a).

⁸⁰ 50 C.F.R. § 402.14(a).

⁸¹ U.S. Environmental Protection Agency 2013, Office of Chemical Safety and Pollution Prevention- Office of Pesticide Programs, *Enhancing Stakeholder Input in the Pesticide Registration Review and ESA Consultation Processes and Development of Economically and Technologically Feasible Reasonable and Prudent Alternatives*, at 8 (Mar. 19, 2013), available at Docket ID EPA-HQ-OPP-2012-0442-0038.

any effects on listed species or designated critical habitat.”⁸² This inquiry even includes beneficial effects. The phrase “may affect” has been interpreted broadly to mean that “any possible effect, whether beneficial, benign, adverse, or of an undetermined character, triggers the formal consultation requirement.”⁸³ For this initial stage of review, exposure to a pesticide does not require that effects reach a pre-set level of significance or intensity to trigger the need to consult (e.g. effects do not need to trigger population-level responses). As the Services’ joint consultation handbook explains, an action agency such as EPA may make a “no effect” determination, and thus avoid undertaking informal or formal consultations, only when “the action agency determines its proposed action will not affect listed species or critical habitat.”⁸⁴

Because the use of these pesticide formulations and products “may affect” listed species and “may affect” the critical habitat of listed species, EPA must consult with the Services regarding its pesticide approvals in order to comply with the ESA.

Fortunately the National Academy of Sciences (“NAS”) has provided guidance regarding the obligations of EPA and other wildlife agencies in analyzing pesticide approvals under the ESA. The NAS committee provided a report to EPA and Services in April of 2013 providing specific recommendations relating to the use of “best available data;” methods for evaluating sublethal, indirect, and cumulative effects; the state of the science regarding assessment of mixtures and pesticide inert ingredients; the development, application, and interpretation of results from predictive models; uncertainty factors; and what constitutes authoritative geospatial and temporal information for the assessment of individual species, habitat effects and probabilistic risk assessment methods.⁸⁵

While the NAS report outlines areas for all three agencies to improve, the NAS report made several significant conclusions about the current ecological risk assessment process and its use of risk quotients (“RQs”), including:

- The EPA “concentration-ratio approach” for its ecological risk assessments “is ad hoc (although commonly used) and has unpredictable performance outcomes.”⁸⁶

⁸² U.S. Fish and Wildlife Service and National Marine Fisheries Service, *Endangered Species Consultation Handbook: Procedures for Conducting Consultation and Conference Activities Under Section 7 of the Endangered Species Act*, at xvi (1998) (hereafter CONSULTATION HANDBOOK) (emphasis in original).

⁸³ *Western Watersheds Project v. Kraayenbrink*, 632 F.3d 472, 496 (9th Cir. 2011) (finding that the threshold for triggering ESA consultation “is relatively low”) (quoting 51 Fed. Reg. at 19,949); *see also Lockyer v. U.S. Dep’t of Agric.*, 575 F.3d 999, 1018 (9th Cir. 2009).

⁸⁴ CONSULTATION HANDBOOK at 3-13.

⁸⁵ National Academy of Sciences, *Assessing Risks to Endangered and Threatened Species from Pesticides*, Committee on Ecological Risk Assessment under FIFRA and ESA Board on Environmental Studies and Toxicology Division on Earth and Life Studies National Research Council (Apr. 30, 2013) (hereafter NAS REPORT).

⁸⁶ *Id.* at 107.

- “RQs are not scientifically defensible for assessing the risks to listed species posed by pesticides or indeed for any application in which the desire is to base a decision on the probabilities of various possible outcomes.”⁸⁷
- “The RQ approach does not estimate risk...but rather relies on there being a large margin between a point estimate that is derived to maximize a pesticide’s environmental concentration and a point estimate that is derived to minimize the concentration at which a specified adverse effect is not expected.”⁸⁸
- “Adding uncertainty factors to RQs to account for lack of data (on formulation toxicity, synergy, additivity, or any other aspect) is unwarranted because there is no way to determine whether the assumptions that are used overestimate or underestimate the probability of adverse effects.”⁸⁹

According to the NAS, the EPA concentration-ratio approach contrasts sharply with a probabilistic approach to assessing risk, which the NAS describes as “technically sound.” The NAS’s underlying conclusion is that EPA should move towards a probabilistic approach based on population modeling, an approach that the NMFS already utilizes.⁹⁰ The NAS also recommends that the FWS move towards a probabilistic approach in its consultations.

Following the publication of the NAS report, the agencies have developed two policy documents to guide consultations on pesticide review and approvals moving forward: (1) *Enhancing Stakeholder Input in the Pesticide Registration Review and ESA Consultation Processes*,⁹¹ and (2) *Interim Approaches for National-level Pesticide Endangered Species Act Assessments Based on Recommendations of the National Academy of Science April 2013*.⁹² The agencies made clear at a November 15, 2013 public meeting that these new procedures and approaches would be “day forward” in their implementation.⁹³ Accordingly, approvals of pesticides and uses *must* follow these new *Interim Approaches* and comply with the requirements of the ESA.

⁸⁷ *Id.* at 11.

⁸⁸ *Id.*

⁸⁹ *Id.*

⁹⁰ *Id.* at 107.

⁹¹ EPA, Office of Chemical Safety and Pollution Prevention- Office of Pesticide Programs, *Enhancing Stakeholder Input in the Pesticide Registration Review and ESA Consultation Processes and Development of Economically and Technologically Feasible Reasonable and Prudent Alternatives* (March 19, 2013), *available at* Docket ID EPA-HQ-OPP-2012-0442-0038.

⁹² *Available at* <https://www.epa.gov/sites/production/files/2015-07/documents/interagency.pdf>

⁹³ INTERAGENCY APPROACH FOR IMPLEMENTATION OF NATIONAL ACADEMY OF SCIENCES REPORT: ASSESSING RISKS TO ENDANGERED AND THREATENED SPECIES FROM PESTICIDES, Public Meeting Silver Spring NOAA Auditorium (Nov. 15, 2013).

A. Completion of Step One under Interim Approaches

As laid out in the National Academy of Sciences and *Interim Approaches* guidance, the risk assessment and consultation process should follow three steps.⁹⁴ These steps generally follow the three inquiries of the ESA consultation process: (1) the “no effect”/ “may affect” determination (2) the “not likely to adversely affect”/ “likely to adversely affect” determination (3) the jeopardy/no jeopardy and adverse modification/no adverse modification of critical habitat determination. Step One generally follows the requirements of the ESA and will in most cases identify those species at risk from pesticides that need additional review through the informal and formal consultation process. At Step One, EPA must gather sufficient data to complete the following two related inquiries: (1) EPA must determine whether pesticide use areas will overlap with areas where listed species are present, including whether a use area overlaps with any listed species’ critical habitat (2) EPA must determine whether off-site transport of pesticides will overlap with locations where listed species are present and/or critical habitat is designated. Off-site transport must include considerations of downstream transport due to runoff as well as downwind transport due to spray drift when the best available science indicates such transport is occurring.⁹⁵

What EPA should do to meet the legal requirements of the ESA is use the best available spatial data regarding the pesticide use patterns and the distribution and range of listed species to determine whether a pesticide’s use overlaps with species, and then make a “may affect”/“no effect” determination. The Fish and Wildlife Service ECOS website provides GIS-based data layers for each listed species with designated critical habitat.⁹⁶ These maps are scalable and can achieve the precision needed to make accurate effects determinations regarding whether a pesticide will have “no effect” or “may affect” a listed species and are certainly accurate enough to make determinations as to whether the use of a pesticide represents adverse modification of critical habitat. Figure One provides an overlay map from ECOS of all critical habitat that has been designated for listed species thus far.

Other sources provide additional data on the distribution and life history of threatened and endangered species. NatureServe provides detailed life history information, including spatial

⁹⁴ NAS REPORT at 37-38.

⁹⁵ The Center acknowledges that in many areas, atmospheric transport is difficult to model and assess. However, in some areas, the impacts of atmospheric transport of pesticides are well understood. A recent study found that a variety of pesticides are accumulating in the Pacific chorus frogs (*Pseudacris regilla*) through atmospheric deposition at remote, high-elevation locations in the Sierra Nevada mountains, including in Giant Sequoia National Monument, Lassen Volcanic National Park, and Yosemite National Park. Smalling, K.L., et al., *Accumulation of Pesticides in Pacific Chorus Frogs (Pseudacris regilla) from California’s Sierra Nevada Mountains*, Environmental Toxicology and Chemistry, 32:2026–2034 (2013).

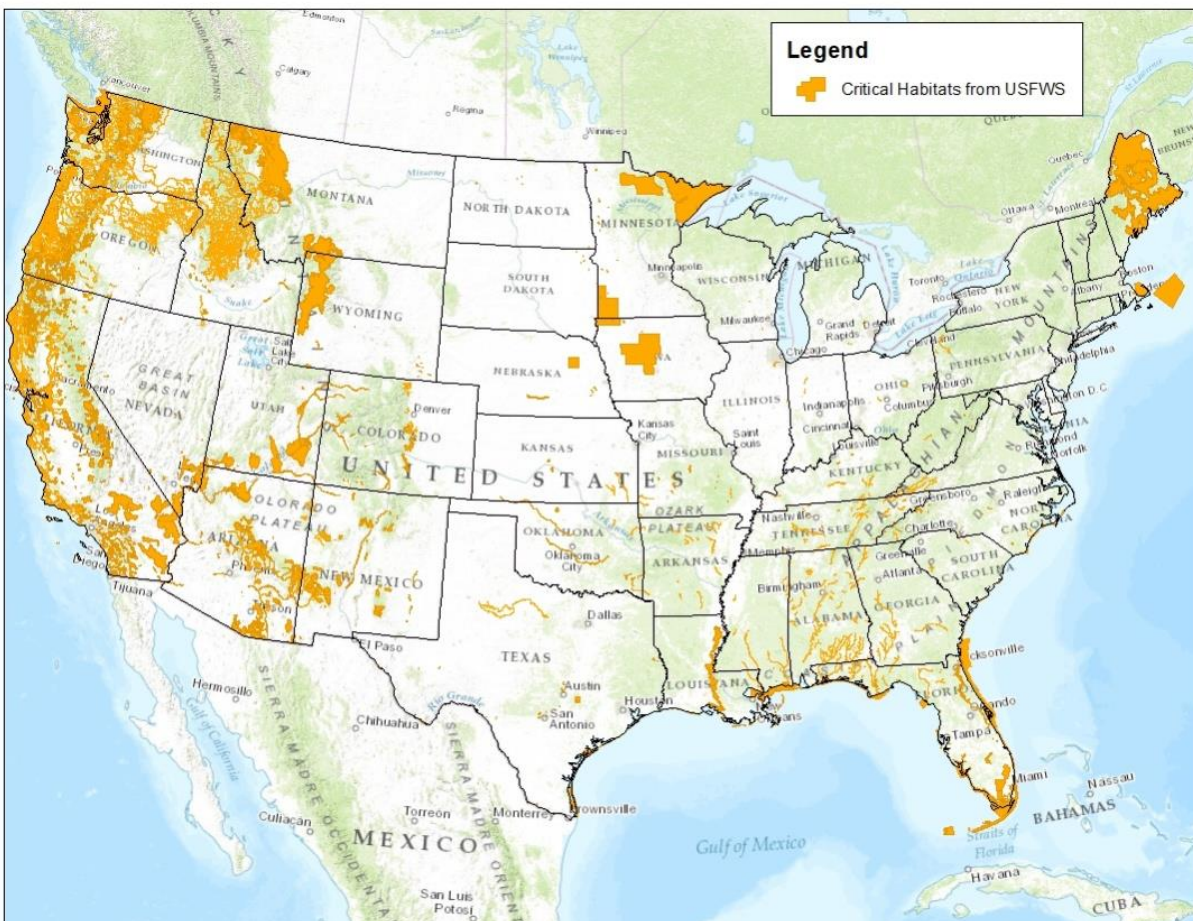
⁹⁶ US Fish and Wildlife Service Environmental Conservation Online System, available at <http://ecos.fws.gov>

distribution, for native species across the United States.⁹⁷ In addition, many State governments collect detailed information on non-game species through their State Wildlife Action Plans.⁹⁸ In short, there are many sources of data that can provide EPA with the detailed information it needs to conduct an effects determination for each species. If there is a subset of species where it believes information is still lacking, EPA should make that clear to all stakeholders which species specifically it believes such data are lacking early in the process such that this information can be collected from the Services and other sources.

⁹⁷ NatureServe Get data, *available at* <http://www.natureserve.org/getData/index.jsp>

⁹⁸ State Wildlife Action Plans, *available at* <http://teaming.com/state-wildlife-action-plans-swaps>

Figure One – Base Composite Map of Critical Habitat in the United States⁹⁹



To make scientifically valid effects determinations, EPA will also need the best available spatial data regarding the use of pesticides. The U.S. Department of Agriculture and the U.S. Geological Survey¹⁰⁰ collect data on an enormous suite of pesticide active ingredients each year, as do several private organizations. Thus, it should be possible to determine where areas of geographic overlap between species and pesticide usage occur. If empirical data on pesticide use or persistence in the environment is lacking geospatial modeling can be used to determine where pesticide use may overlap with affected endangered species.

With the completion of the problem formulations for Ecological Risk, EPA should now move quickly to begin the informal consultation process for pesticides, starting with a spatial analysis as envisioned as Step one. If this information is collected and assessed properly, then it should then be relatively straightforward for EPA to begin to develop geographic restriction on the use

⁹⁹ US Fish and Wildlife Service Environmental Conservation Online System, *available at* <http://ecos.fws.gov>

¹⁰⁰ USGS, National Water-Quality Assessment Program, Pesticide National Synthesis Project, Annual Pesticide Use Maps: 1992-2013, *available at* <https://water.usgs.gov/nawqa/pnsp/usage/maps/>

of pesticides wherever designated critical habitat for a listed species exists as parts of Step Two and Step Three. However, because not all threatened and endangered species have critical habitat, EPA will also have to collect data on the distribution and range of species that do not yet have critical habitat to determine whether the use of these pesticides will jeopardize any of those species.

B. Label Requirements.

FIFRA requires that EPA evaluate and reregister a pesticide every 15 years. During that 15 year period, crop distributions change, use patterns for pesticides change, and listed species change. By the time the registration review process is complete several years from now, additional species will almost certainly be protected by the ESA. Of the species currently listed, some may move towards recovery and become more common while others may become even more imperiled.

Product labels must be able to adapt to changing conditions on the ground to ensure that the use of these pesticides do not cause unanticipated adverse impacts that result in levels of take not authorized through the Section 7 consultation process. Fortunately, the EPA has already developed a system that can address impacts to endangered species and that provides for geographically-targeted conservation measures on the ground through its *Bulletins Live! Two* website.¹⁰¹ The Center recommends that whenever a pesticide may affect listed species, both as a precautionary matter and as a mechanism to implement any conservation measures that are implemented in the informal and formal consultation process, EPA use the *Bulletins Live! Two* system to incorporate these measures. Accordingly, all product labels for pesticides affecting endangered species must contain the following language:

This product may have effects on federally listed threatened or endangered species or their critical habitat in some locations. When using this product, you must follow the measures contained in the Endangered Species Protection Bulletin for the county or parish in which you are applying the pesticide. To determine whether your county or parish has a Bulletin, and to obtain that Bulletin, consult <http://www.epa.gov/espp/>, or call 1-800-447-3813 no more than 6 months before using this product. Applicators must use Bulletins that are in effect in the month in which the pesticide will be applied. New Bulletins will generally be available from the above sources 6 months prior to their effective dates.¹⁰²

¹⁰¹ U.S. Environmental Protection Agency Endangered Species Protection Bulletins, available at <http://www.epa.gov/espp/bulletins.htm>

¹⁰² *Endangered Species Protection Program Field Implementation*, 70 Fed. Reg. 66392 (Nov. 2, 2005).

II. EPA Must Make Defensible “Not Likely to Adversely Affect” and “Likely to Adversely Affect” Determinations as a Prerequisite for Defensible “Jeopardy” and “No Jeopardy” Determinations.

At the informal consultation stage, EPA must determine whether the use of a pesticide is either “not likely to adversely affect” (“NLAA”) a listed species or is “likely to adversely affect” (“LAA”) a listed species.¹⁰³ The Services define NLAA as “when effects on listed species are expected to be discountable, insignificant, or completely beneficial.” Discountable effects are those that are extremely unlikely to occur and that the Services would not be able to meaningfully measure, detect, or evaluate” because of their insignificance¹⁰⁴ In the context of pesticides, only if predicted negative effects are discountable or insignificant can EPA avoid the need to enter formal consultations with the Services. This is *not* a high threshold. EPA is not required to make a determination as to whether exposure to a pesticide results in population level changes in order to request formal consultations. The Center believes that the Step Two approach described is generally compatible with the mandates of the ESA regarding actions that may affect listed species. The one in a million mortality threshold for “likely to adversely affect” reflects the ESA’s and the Consultation Handbook’s requirements. The decision to consider 1) sublethal effects to species, 2) additive, synergistic and cumulative effects of all chemicals and non-chemical stressors present in the pesticide formulation, tank mixture, and the environment, 3) and the fate and action of pesticide degradates at Step Two is also consistent with the ESA’s requirements and represents an important change from the previous EPA approach, in which EPA was making policy judgments at Step Two as to whether known, adverse, population-level impacts crossed a severity threshold to warrant consultations.

Finally, the Center notes that at Step Three, the formal consultation process, EPA and Services must consider the environmental baseline as well as all cumulative effects when determining if the approval pesticides, formulations, or uses will jeopardize any threatened or endangered species. The Services define environmental baseline as “the past and present impacts of all Federal, State, or private actions and other human activities in an action area, the anticipated impacts of all proposed Federal projects in an action area that have already undergone formal or early section 7 consultation, and the impact of State or private actions that are contemporaneous with the consultation in process.”¹⁰⁵ Cumulative effects are defined as “those effects of future State or private activities, not involving Federal activities, that are reasonably certain to occur within the action area of the Federal action subject to consultation.”¹⁰⁶ Pesticide consultations

¹⁰³ U.S. Fish and Wildlife Service and National Marine Fisheries Service, *Endangered Species Consultation Handbook: Procedures for Conducting Consultation and Conference Activities Under Section 7 of the Endangered Species Act*, at 3-1 (1998).

¹⁰⁴ *Id.* at xv.

¹⁰⁵ *Id.* at xiv.

¹⁰⁶ *Id.* at xiii.

must consider the interactions between the active ingredient under review and other pollutants in the present in the environment.

Pesticide and their residues and degradates do not occur in single exposure situations and many different mixtures of pesticides occur in water bodies at the same time.¹⁰⁷ The mixtures of these chemicals can combine to have additive or synergistic effects that are substantially more dangerous and increase the toxicity to wildlife.¹⁰⁸ Thus, to fully understand the ecological effects and adverse impacts, EPA and the Services must consider the pesticide's use in the context of *current* water quality conditions nationwide. In particular, the use of pesticides in watersheds that contain threatened or endangered species and where water quality is already impaired could be particularly problematic. Therefore, the agencies must use the best available data to fully inform its ecological risk assessment by considering water quality.

In conclusion, EPA should move quickly to assemble the needed spatial data to make an informed “no effect” or “may affect” finding for *each* listed species that will likely overlap with the use of these pesticides or come into contact with its environmental degradates. If there is overlap, EPA must at a minimum conclude that the use of these pesticides “may affect” listed species. Where this occurs, EPA has a choice—(1) EPA can elect to complete an informal consultation through a biological assessment (also known as a biological evaluation), or (2) EPA can undergo formal consultation with the Services. If EPA completes a biological assessment and implements geographically-tailored conservation measures through *Bulletins Live! Two*, it may be able to reach NLAA determinations via the informal consultation process and alleviate the need for formal consultations. In the alternative, EPA can move directly to formal consultation after making “may affect” determinations for species where the impacts of pesticides are more complex and will take additional expertise to develop sufficient conservation measures. Cumulative effects need to be measured in Steps 2 and 3.

III. EPA and the Services Must Assess the Adverse Impacts on Critical Habitat.

Section 7 of the ESA prohibits agency actions that would result in the “destruction or adverse modification of [critical] habitat.”¹⁰⁹ This inquiry is separate and distinct from the question as to whether a pesticide approval will result in jeopardy to any listed species. A no jeopardy finding (or a Not Likely to Adversely Affect finding in an informal consultation) is *not* equivalent to a

¹⁰⁷ NMFS, *Endangered Species Act Section 7 Consultation Draft Biological Opinion for the Environmental Protection Agency's Pesticide General Permit for Discharges from the Application of Pesticides* at 118-119, lines 4209-31 (2011) (hereafter Draft BiOp); Gilliom, R.J. et al., *Pesticides in the Nation's Streams and Ground Water, 1992–2001—A Summary* (2006), available at <http://pubs.usgs.gov/fs/2006/3028/>.

¹⁰⁸ Draft BiOp at 127-129, lines 4471-4515; Gilliom, R.J., *Pesticides in the Nation's Streams and Ground Water*; Environmental Science and Technology, 413408–3414 (2007).

¹⁰⁹ 16 U.S.C. § 1536(a)(2).

finding that critical habitat will not be adversely modified. While there is much overlap between these two categories (for example, as in *Tennessee Valley Authority v. Hill*¹¹⁰ where the proposed agency action to build a dam would both destroy a species' habitat and kill individual members of the species in the same time) many agency actions do result in adverse modification to critical habitat without causing direct harms to species that do rise to the level of jeopardy.¹¹¹ Indeed, the ESA's prohibition on "destruction or adverse modification" of critical habitat does not contain any qualifying language suggesting that a certain species-viability threshold must be reached prior to the habitat modification prohibition coming into force.

As three federal circuit courts have made abundantly clear, avoiding a species' immediate extinction is not the same as bringing about its recovery to the point where listing is no longer necessary to safeguard the species from ongoing and future threats. Therefore, Section 7 requires that critical habitat not be adversely modified in ways that would hamper the *recovery* of listed species.¹¹² These potent pesticides with known adverse ecological effects have the potential to adversely modify critical habitat by altering ecological community structures, impacting the prey base for listed species, and by other changes to the physical and biological features of critical habitat. Accordingly, the informal consultation must separately evaluate whether these pesticide products and formulations will adversely modify critical habitat regardless of whether these pesticide products jeopardize a particular listed species. For example, if plant communities alongside a water body that has been designated as critical habitat suffer increased mortality, and this then results in increased temperatures or increased sedimentation, that would represent adverse modification of critical habitat. Likewise, if pesticides are toxic to species lower in the food chain, and a threatened or endangered species feeds on those affected prey species, this impact to the food web would represent a clear example of adverse modification to critical habitat.

EPA's evaluation must address impacts to critical habitat even if the direct effects on listed species fall below the NLAA or jeopardy thresholds. The Center recommends that EPA design conservation measures—and implement those measures using *Bulletins Live! Two*—specifically to protect critical habitat of listed species from exposure to pesticides, and where appropriate, prohibit its use altogether in critical habitat where necessary. Doing so would provide meaningful, on-the-ground protections for hundreds of listed species, and may in some cases, help EPA and the Services then reach a defensible NLAA or "no jeopardy" opinion.

¹¹⁰ 437 U.S. 153 (1978)

¹¹¹ See Owen, D., *Critical Habitat and the Challenge of Regulating Small Harms*. Florida Law Review 64:141-199 (2012).

¹¹² See *Gifford Pinchot Task Force v. FWS*, 378 F.3d 1059, 1069-71 (9th Cir. 2004) (finding a FWS regulation conflating the requirements of survival and recovery to be unlawful); see also *N.M. Cattle Growers Ass'n v. FWS*, 248 F.3d 1277, 1283 n.2 (10th Cir. 2001); *Sierra Club v. FWS*, 245 F.3d 434, 441-42 (5th Cir. 2001)

IV. EPA Has an Independent Duty Under the Endangered Species Act to Consult with the U.S. Fish and Wildlife Service and National Marine Fisheries Service on the Approval of All End-use Product Labels.

Just as EPA must consult with the Services regarding the reregistration of an active pesticide ingredient, EPA must also consult with the Services regarding the registration or approval of end use and technical pesticide products. Such consultations must also occur at the earliest possible time to ensure that specific product formulations do not result in jeopardy for a listed species or adversely modify critical habitat.

In addition, because end use formulations may result in mixes of the active ingredient with “other ingredients” before application, EPA must consider during the consultation process the effects of these “inert” or “other” ingredients together with the active ingredient on listed species and set appropriate conservation restrictions accordingly. As noted in *Washington Toxics Coalition v. U.S. Dept. of Interior*, “other ingredients” within a pesticide end product may cause negative impact to listed species even if they are less toxic than the active ingredient being reviewed.¹¹³ “Other ingredients,” such as emulsifiers, surfactants, anti-foaming ingredients, and fillers may harm listed species and adversely modify critical habitat. Many of the more than 4,000 potentially hazardous additives allowed for use as pesticide additives are environmental contaminants and toxins that are known neurotoxins and carcinogens.¹¹⁴ EPA has routinely failed to consult with the Services on the registration of “other ingredients,” potentially compounding harms to listed species by allowing such ingredients to be introduced widely into the environment. EPA must, as part of the consultation process, consider the range of potential impacts by using different concentrations and different formulations of the active ingredient, as well as the potential negative impacts of “other ingredients” used in end use products.

The National Academy of Science report recognized that without real-world considerations of where listed species are located, the relative conservation status of listed species, the environmental baseline, and the interaction of pesticides with other active ingredients, pesticide degradates, and other pollutants, the EPA risk assessment process will not be able to make meaningful predictions about which endangered species will be adversely affected. Until EPA can conduct realistic assessments, it should take a precautionary approach and enter into formal consultations with the Services as outlined in the *Interim Approaches* document.

¹¹³ 457 F. Supp. 2d 1158 (W.D. Wash 2006).

¹¹⁴ Draft BiOp at 113, lines 4062-68; 120-121, lines 4262-308; 127, lines 4445-4455; Northwest Coalition for Alternatives to Pesticides, et al., Petition to Require Disclosure of Hazardous Inert Ingredients on Pesticide Product Labels (2006), available at http://www.epa.gov/opprd001/inerts/petition_ncap.pdf.