



*Via Regulations.gov*

May 10, 2017

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

**Re: Comments on EPA's Receipt of Application for New Use – Oxytetracycline Calcium  
(Docket #: EPA-HQ-OPP-2016- 0754; EPA Reg. #: 55146-97, 55149-99)**

The Center for Biological Diversity (Center) and Johns Hopkins Center for a Livable Future (CLF) submit the following comments in response to the Environmental Protection Agency's (EPA) receipt and review of an application to register a new use under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of the pesticide product oxytetracycline calcium for use on citrus crop group 10-10; citrus, dried pulp. The Center is a national, nonprofit organization with more than 1.3 million members and online activists that is dedicated to the protection of rare and imperiled species and the habitats on which they rely. CLF works with students, educators, researchers, policymakers, advocacy organizations, and communities to build a healthier, more equitable, and resilient food system.

Due to concerns about public health, wildlife safety, and the environment, commenters strongly oppose the proposed expanded use of oxytetracycline calcium, an antibiotic that is highly important to human medicine and the subject of antibiotic resistance concerns. If EPA wishes to continue pursuing this application, however, 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 necessary factors into its evaluation and any proposed decision; and
4. Placing appropriate restrictions on uses to avoid and minimize adverse effects.

## DETAILED COMMENTS

### **I. EPA should Deny the Application to Register New Uses of Oxytetracycline Calcium**

It is wholly inappropriate and against sound science for EPA to continue to approve the use of medically-important antibiotics such as oxytetracycline to be used for prophylactic pesticidal purposes, including for controlling citrus greening.

Oxytetracycline is a member of the tetracycline class of antibiotics, a group of human and animal broad-spectrum antibiotics. Historically, tetracyclines have been characterized by their efficiency against a wide range of Gram-positive and Gram-negative bacteria, with oxytetracycline relied upon in human and veterinary medicine to treat bacterial diseases and as an alternative antibiotic for people allergic to penicillin. Oxytetracycline is also used as a second line of defense for bacteria that pose significant health threats, such as anthrax. Medicines containing oxytetracycline are dispensed with a prescription from a physician.

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.<sup>1</sup> 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 tetracycline class - including oxytetracycline - is ranked in that list as being "highly important" to human medicine.<sup>2</sup> In 2005, the World Health Organization (WHO) developed similar criteria for ranking medically important antibiotics; on the WHO list, tetracyclines were again ranked as "highly important."<sup>3</sup>

Antibiotics such as oxytetracycline 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 improve, rather than degrade, the safety and efficacy of these drugs.<sup>4</sup> In part, that prioritization is the result of the growing problem of antibiotic resistance, a concern that is held both domestically and internationally.<sup>5</sup>

The misuse and abuse of antibiotics is one of the single most important and preventable factors contributing to and accelerating the spread of antibiotic resistance around the world.<sup>6</sup> Bacterial resistance to oxytetracycline as a result of 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."<sup>7</sup>

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

---

<sup>1</sup> 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).

<sup>2</sup> *Id.*

<sup>3</sup> World Health Organization (WHO), *Critically Important Antimicrobials for Human Medicine*, 5th Revision (2016), available at <http://apps.who.int/iris/bitstream/10665/255027/1/9789241512220-eng.pdf?ua=1>.

<sup>4</sup> 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 (CDC), *Antibiotic resistance threats in the United States, 2013* (2013), available at <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>.

<sup>5</sup> 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).

<sup>6</sup> 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).

<sup>7</sup> CDC, *The Core Elements of Hospital Antibiotic Stewardship Protection*, available at <https://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>.

Combating Antibiotic-Resistance Bacteria, and directed that agencies - including the EPA - work together to detect, prevent, and control antibiotic resistance through strategic, coordinated, and sustained efforts.<sup>8</sup> 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*.<sup>9</sup>

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.<sup>10</sup> 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.<sup>11</sup> In that 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."<sup>12</sup> Despite the change in the administration domestically, these 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 performed to the exclusion of incorporating similar stewardship objectives and burdens into 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.

---

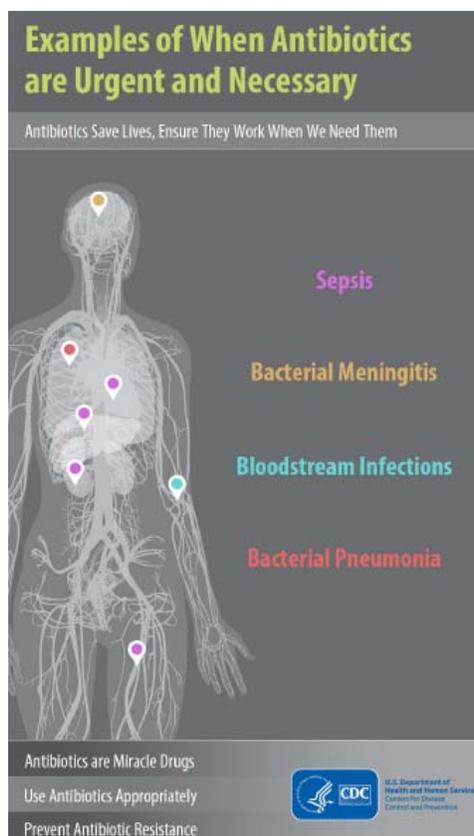
<sup>8</sup> Exec. Order No. 13,676, Combating Antibiotic-Resistant Bacteria, 79 Fed. Reg. 56,931 (Sept. 18, 2014).

<sup>9</sup> *Id.* (emphasis added).

<sup>10</sup> 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).

<sup>11</sup> WHO, *Global Action Plan on Antimicrobial Resistance* (2015), available at [http://www.wpro.who.int/entity/drug\\_resistance/resources/global\\_action\\_plan\\_eng.pdf](http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf).

<sup>12</sup> *Id.* at i.



CDC, *Examples of When Antibiotics are Urgent and Necessary* (2013)

In addition to threatening human health and economic security, antibiotic abuse threatens environmental health and safety, as well as endangers exposed wildlife and other creatures. Knowledge 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.<sup>13</sup>

Oxytetracycline is understood to be relatively persistent in the environment, with data indicating biodegradation to be slow. For example, a study by Cengiz, *et al.*, evidenced the ongoing presence of

<sup>13</sup> 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).

oxytetracycline in agricultural soils for 10 months,<sup>14</sup> while another study by Halling-Sorensen, *et al.*, indicated that oxytetracycline compounds can remain present in soil interstitial waters from 2 to 270 days.<sup>15</sup> Further, since oxytetracycline demonstrates tight adhesion to soil particles, the presence of this drug in aquatic environments further compounds the risk, and can lead to the contamination of local sediments and stream beds, which can affect both current and future environment and species health.<sup>16</sup>

Antibiotic-resistant bacteria can also spread through contaminated soil and water.<sup>17</sup> Since unintended exposures is common with pesticide use, this proposal signifies a serious potential for adverse reaction with no clinical benefit.

All pesticides sold or used in the U.S. must be registered by the EPA and based on scientific studies showing that they can be used without posing unreasonable effect on public health or the environment.<sup>18</sup> Here, substantial evidence indicates that such harm will occur if this application is accepted and the new proposed uses of oxytetracycline calcium approved. In light of these critical concerns, the agency should deny this application.

## **II. EPA Cannot Authorize any Additional Uses of Oxytetracycline Calcium as Pesticide before First Complying with its Duties under the Endangered Species Act and FIFRA**

In addition, before EPA can make any supportable decision to authorize additional uses of this antibiotic as a pesticide, it must first accomplish all of the following:

### **A. EPA Must Comply with its Duties under Section 7 of the Endangered Species Act, including Completion of Consultation.**

EPA must insure that the approved uses of this pesticide do not jeopardize species protected by the ESA or adversely modify or destroy their critical habitat. As a separate, discretionary action that may affect endangered and threatened species, EPA cannot approve new uses prior to the completion of consultations with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (the Services).<sup>19</sup> Without such consultation, EPA cannot satisfy its duty to insure that its action does not jeopardize the continued existence of imperiled species across the country or adversely modify or destroy their critical habitat. Moreover, unless and until the EPA completes ESA consultation, any taking of protected species from the use of this pesticide is unlawful.

---

<sup>14</sup> Cengiz, *et al.*, *Detection of Oxytetracycline and Chlortetracline Residues in Agricultural Fields in Turkey*, 4(10) J. Biol. Env'tl. Sci. 23 (2010).

<sup>15</sup> Halling-Sorensen, *et al.*, *Characterization of the Abiotic Degradation Pathways of Oxytetracycline in Soil Interstitial Water Using LC-MS-MS*, 50 Chemosphere 1331 (2003).

<sup>16</sup> See, e.g., Ingerslev, *et al.*, *Occurrence, Fate, and Effects of Pharmaceutical Substances in the Environment - A Review*, 36 Chemosphere 357 (1998); Berlind and Jacobsen, *Persistence of Oxytetracycline in Sediments from Fish Farms*, 70 Aquaculture 365 (1988).

<sup>17</sup> 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 Env'tl Sci. Pollution Res. 11729 (2014).

<sup>18</sup> 7 U.S.C. § 136a(c)(5); see also *Reckitt Benckiser Inc. v. EPA*, 613 F.3d 1131, 1133 (D.C. Cir. 2010).

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

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.”<sup>20</sup> The ESA's implementing regulations broadly construe "agency action" to include licensing and permitting actions.<sup>21</sup>

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.<sup>22</sup> 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.<sup>23</sup> The EPA must initiate consultation under Section 7 whenever its action “may affect” a listed species or critical habitat.<sup>24</sup> 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.”<sup>25</sup> Accordingly, the EPA must consult with the Services on its continuing and ongoing authority over this pesticide to satisfy its duty to insure that its use will not jeopardize or adversely modify protected species or their critical habitat *before* it allows expanded use of this antibiotic-pesticide.

Specifically, EPA must consult on the adverse effects of this antibiotic-pesticide, as discussed further in Section I, and all synergistic and cumulative uses. Regarding synergistic and cumulative uses, expanding the range of crops that this antibiotic is approved for use upon will likely expand the total amount of antibiotic-pesticides being used in any given period of time. Since oxytetracycline calcium may be applied with other pesticides, its increased application may experience 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.<sup>26</sup>

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

---

<sup>20</sup> 16 U.S.C. § 1536(a)(2) (emphasis added).

<sup>21</sup> 50 C.F.R. § 402.02(c).

<sup>22</sup> 50 C.F.R. § 402.14(a).

<sup>23</sup> EPA, *Enhancing Stakeholder Input in the Pesticide Registration Review and ESA Consultation Process and Development of Economically and Technologically Feasible Reasonable and Prudent Alternatives*, EPA Docket No. EPA-HQ-OPP-2012-0442, 7 (Mar. 19, 2013).

<sup>24</sup> 50 C.F.R. § 402.14(a).

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

<sup>26</sup> *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)).

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.<sup>27</sup>

#### **B. EPA must Require that the Registrant Provide all Necessary Data and Studies.**

EPA must have substantial evidence to approve a new use. To do so, EPA must require all necessary data and studies, including, but not limited to, any previously identified data or study gaps; additional studies to evaluate effects on imperiled species, including on pollinators in accordance with the *Guidance for Assessing Pesticide Risks to Bees*;<sup>28</sup> information concerning antibiotic resistance and estrogen or other endocrine disruption effects;<sup>29</sup> and any information that this antibiotic-pesticide or products containing this antibiotic-pesticide may have synergistic effects.

This requirement is especially critical here because of the greatly increasing use amounts that will necessarily accompany this approval, heightened antibiotic resistance concerns, and limitations in previous assessments of the environmental and public health effects of this antibiotic when used as a pesticide.

#### **C. EPA must Incorporate Necessary Factors into its Evaluation and any Proposed Decision.**

EPA must incorporate necessary factors into its evaluation and any proposed decision. These factors should include, at a minimum, the following:

- a. effects on species listed as protected under the ESA and their critical habitat,
- b. effects on pollinators and other beneficial insects,
- c. effects on human health or environmental safety concerning antibiotic resistance, and
- d. any additive, cumulative or synergistic effects of the use of this pesticide.

#### **D. EPA must Place Appropriate Restrictions on Uses 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 extremely concerning nature of approving a medically-important antibiotic for use as a pesticide, both generally and specifically as it relates to this application, EPA must use its authority to place appropriately restrictive limitation on the use of this antibiotic as a pesticide to avoid and minimize adverse effects.

---

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

<sup>28</sup> 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](https://www.epa.gov/sites/production/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf); see also Raymann, *et al.*, *Antibiotic Exposure Perturbs the Gut Microbiota and Elevates Mortality in Honeybees*, 15(3) PLoS Biol. e2001861 (2017) (found that the common antibiotic tetracycline used - at below field levels - resulted in altered be gut micorbiota that is linked to reduce fitness, decreased survival rates, and increase susceptibility to pathogens); Hamdi, *et al.*, *Gut Microbiome Dysbiosis and Honeybee Health*, 135 (7) Journal of Applied Entomology 524 (2011).

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

## CONCLUSION

Commenters strongly believe in a livable and sustainable future, and the importance of a resilient and just food system. The Center has worked since its inception to protect imperiled plants and wildlife, open space, air and water quality, and overall quality of life. The Center's Environmental Health Program aims to secure programmatic changes in the pesticide registration process and to stop toxic pesticides from contaminating fish and wildlife habitats and harming public health and the environment. We appreciate the opportunity to provide comment.

Respectfully submitted,

**Hannah Connor**

Senior Attorney  
Environmental Health Program  
Center for Biological Diversity

**Keeve E. Nachman, PhD, MHS**

Assistant Professor  
Department of Environmental Health and Engineering  
Johns Hopkins Bloomberg School of Public Health  
Director, Food Production and Public Health Program  
Johns Hopkins Center for a Livable Future  
Co-Director, Johns Hopkins Risk Sciences and Public Policy Institute

**Robert Martin**

Senior Lecturer, Department of Environmental Health & Engineering  
Johns Hopkins Bloomberg School of Public Health  
Program Director, Food System Policy  
Johns Hopkins Center for a Livable Future  
Johns Hopkins University