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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 on the Concept for a Framework to Assess the Risk to the Effectiveness of Human and Animal Drugs Posed by Certain Antibacterial or Antifungal Pesticides (Docket # EPA-HQ-OPP-2023-0445)

The undersigned organizations submit the following comments on the concept paper developed by the U.S. Environmental Protection Agency (EPA), The U.S. Department of Health and Human Services (HHS), and the U.S. Department of Agriculture (USDA), for a framework to assess antimicrobial resistance (AMR) concerns arising from the use of pesticides (hereafter referred to as the "Concept Note"). Together, we represent millions of Americans deeply concerned about AMR developing in human pathogens and the health impact that the use of certain pesticides can have in perpetuating those concerns.

We appreciate the opportunity to provide comment.

Introduction

AMR is one of the biggest threats to public health in the world, killing over 1.2 million people every year and projected to result in the annual death of 10 million people by 2050.[1] Antimicrobials are lifesaving medicines that transformed healthcare in the 20th century. Effective antimicrobials are essential for surgery, chemotherapy, organ transplantation and the care of premature infants.[2] New resistant pathogens are emerging such as *Candida auris*[3] while the development of new antimicrobials has slowed. [4] Without much greater action, the problem of AMR will only grow.

The urgency of the AMR threat requires that EPA quickly implement a risk analysis framework in this space. An increasing amount of scientific research has implicated the use of bactericides and fungicides in crop agriculture – in particular, as pesticides – as playing an underappreciated role in contributing to the development of pathogens that are resistant to human medicines, particularly antifungals. We appreciate the agency's willingness to tackle this long-neglected problem and urge the EPA to move quickly to ensure the Agency complete its analysis of relevant pesticides in time for registration review deadlines that are fast approaching. If the EPA

[1] https://www.unep.org/explore-topics/chemicals-waste/what-we-do/emerging-issues/antimicrobial-resistance-global-threat
[2] https://pubmed.ncbi.nlm.nih.gov/24252483/
[3] https://www.acpjournals.org/doi/10.7326/M22-3469
[4] https://www.gao.gov/products/gao-22-105042

does not incorporate the framework as part of a pesticide's registration review, we urge the agency to apply the framework to any previously approved pesticides as soon as it is finalized and to implement any necessary label changes as soon as possible. Given the urgency of the AMR crisis, we simply cannot wait to apply the framework in the next registration review cycle (15-20 years from now).

Our groups are deeply concerned about the growing threat of AMR and we have written about and been involved in litigation related to this matter. We thus have a lot of experience and expertise on this subject, much of which is more relevant for the detailed analyses on individual chemicals that will hopefully take place soon. Our comments here will focus on big-picture elements of the Concept Note, addressing the questions and issues set forth in the note.

To Ensure the Framework is Appropriately Defined and Clear to Stakeholders, EPA Must Apply a One Health Approach and Embrace Transparency

It is widely acknowledged in the U.S. and around the world that in order to effectively tackle the threat of AMR, a One Health approach must be adopted when analyzing and implementing AMR risk management options. One Health refers to a collaborative approach that seeks to incorporate expertise from those in different disciplines to simultaneously assess the interconnection between humans, animals, plants/crops, and their shared environment. A One Health approach is in use by the World Health Organization and federal agencies such as the Centers for Disease Control and Prevention (CDC) and U.S. Food and Drug Administration (FDA), among many others.

As currently written, the Concept Note identifies federal partners with varying expertise that EPA will work with to some extent to analyze and implement the elements in the framework, indicating that something resembling a One Health approach may be envisioned. However, the stated collaboration is poorly defined and lacks appropriate transparency.

As EPA finalizes its Concept Note, we ask that the agency explicitly state how each federal partner will be involved in this process moving forward. We firmly believe the EPA does not have the appropriate expertise to accurately define risk in this space without significant help from other federal partners, such as the CDC. For example, some of the undersigned groups commented on EPA's flawed 2021 approval of streptomycin for use as a pesticide on citrus, which EPA did without proper collaboration with federal partners.[5] A successful process must be highly collaborative, respectful of all perspectives and positions, and be highly transparent.

In sum, to ensure the Concept Framework is properly defined and easy for stakeholders to understand, we urge EPA to directly state in the final framework its intention to apply a One Health approach to its analysis and to explicitly state how the expertise of each federal partner will be utilized in assessing AMR threats arising from pesticide use. We believe this is the perfect opportunity to define each agency's role early on in this process and explore how each federal partner's input will be solicited and utilized in EPA's decision-making. EPA must ensure that

[5] https://www.regulations.gov/document/EPA-HQ-OPP-2016-0067-0015; https://www.regulations.gov/comment/EPA-HQ-OPP-2016-0067-0199.

there is transparency about what type of input EPA is receiving from federal partners and how EPA is utilizing that input in its decisions.

To Ensure the Framework is Appropriately Defined and that the Appropriate Pesticides are Evaluated, EPA Must Define the Relevant Drug Classes and the Relevant Pesticides.

We fully support EPA's proposal to analyze resistance to both antibacterials and antifungals used in human medicine in the scope of the framework. A framework that does not include both will fail to account for the full costs of pesticide use and would result in registrations that continue to violate the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

To evaluate the risk of AMR from pesticide use most effectively, there are two categories of chemicals that must be appropriately defined in the framework: the relevant drug classes for which AMR development is a concern and the relevant pesticides that can lead to resistance to the drugs of concern.

a. Definition and Classification of Medically Important Drugs

The goal of the framework is to aid the EPA in assessing and mitigating the risk of pesticide use compromising treatment of infections in humans, animals, and plants. Therefore, EPA must identify which antimicrobial treatments could be impacted. We recommend EPA follow the criteria developed by the FDA described in Appendix A of Draft Guidance #152 to identify which antimicrobials, either antibacterial or antifungal, are medically important along with a ranking of their medical importance.[6] In order to include the antifungals, the FDA criteria should be modified to refer to all antimicrobials not just antibacterials. The criteria then would read:

> 1. Critically important antimicrobials: drugs from an antimicrobial class that are the sole or one of limited available therapies used to treat serious infections in humans.
>
> 2. Highly important antimicrobials: drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat serious infections in humans; that is, drugs from more than a few antimicrobial classes are available; OR, drugs from an antimicrobial class used to treat non-serious infections in humans and are the sole or one of limited available therapies.
>
> 3. Important antimicrobials: drugs from an antimicrobial class used to treat non-serious infections in humans and are NOT the sole or one of limited available therapies; that is, drugs from more than a few antimicrobial classes are available.

Under these criteria all antimicrobials used in human medicine are considered medically important with some ranked as highly and critically important. An alternative ranked list of medically important antibiotics has been developed by the World Health Organization but the criteria for ranking antibiotics includes factors related to the likelihood of transferring resistance

[6] https://www.fda.gov/media/69949/download

from animals to humans which may not be relevant when discussing resistance linked to pesticide use.[7]

There are only four antifungal classes used to treat serious systemic fungal infections: azoles, echinocandins, pyrimidines and polyenes.[8] These are all one of limited therapies for serious infections in humans including the WHO Critical Priority Pathogens *Candida auris*, *Candida albans* *Aspergillis fumigat*a , and *Cryptococcus neoformans*.[9] Under the ranking criteria developed by the FDA all four classes would be ranked as critically important.

Any new classes of antimicrobials under development for use in humans should be considered "critically important" as recommended by the World Health Organization.[10] This should include the DHODH inhibitor class with the drug, olorofim, and the pesticide, ipflufenoquin.[11]

The rankings (important, highly important, critically important) are needed to better characterize the potential impacts of treatment failure due to resistance developing from the use of a pesticide. These impacts should be taken into consideration in the risk assessment during the AMR risk conclusion. The risk determination should then guide the selection of appropriate risk management measures needed to control the threat of resistance resulting from the use of a pesticide.

b. Definition and Classification of Relevant Pesticides to Analyze

We propose that the scope of the Concept Note is as follows:

> All pesticides that have known antibacterial or antifungal activity, as well as any other pesticide that has been found to facilitate resistance to antimicrobials.

Such breadth is a necessary part of a systematic review process. In practice many of these pesticides will be triaged out in the risk characterization phase because they will not belong to classes of medically important medicines or there will not be an established potential pathway to resistance development.

It is important in the Concept Note to recognize that it is not just conventional antibacterials and antifungals that can induce drug resistance in pathogens, but other pesticides can do so as well. For instance, the use of labelled rates of several herbicides have been demonstrated to change drug susceptibility of Salmonella and E. coli,[12] and penicillin resistance of bacteria in crops fields was found to be linked to glyphosate resistance.[13]

The determination of which pesticides to include under the framework should take into consideration co-selection and cross-resistance. Co-selection occurs when there are genetic

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[7] https://www.who.int/publications/i/item/9789241515528

[8] https://www.science.org/doi/10.1126/science.aap7999?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

[9] https://www.who.int/publications/i/item/9789240060241; and https://www.cdc.gov/fungal/diseases/index.html

[10] https://aricjournal.biomedcentral.com/articles/10.1186/s13756-017-0294-9

[11] https://www.sciencedirect.com/science/article/pii/S136876462200084X?via%3Dihub

[12] https://pubmed.ncbi.nlm.nih.gov/25805724/

[13] https://www.sciencedirect.com/science/article/abs/pii/S0261219416302320?via%3Dihub

linkages between genes responsible for antimicrobial resistance and resistance to an unrelated pesticide. For instance, use of metals in agriculture can co-select for resistance to antimicrobial drugs.[14,15] Cross-resistance occurs when resistance arises to multiple chemical agents that share a common mechanism of action (MoA).

Whether through co-resistance, cross-resistance or other mechanism, numerous pesticides not considered antimicrobials have been shown to lead to resistance in bacteria.[16] The scope of the framework must be broad enough to address the risk of AMR created by the use of these pesticides.

Below is a list of a few prominent examples of pesticides that should be analyzed by the framework envisioned in the Concept Note (note: this is not an exhaustive list):

1. Aminoglycosides (streptomycin, kasugamycin)
2. Tetracyclines (oxytetracycline)
3. Quinolones (Oxolinic acid)
4. Metals (copper, zinc, silver and arsenic containing products)
5. Azole fungicides (Tebuconazole, Propiconazole, etc)
6. Dithiocarbamates (Mancozeb, Thiram, Metam sodium, etc.)
7. DHODH inhibitors (Ipflufenoquin)
8. Glyphosate (known antibiotic MoA and evidence of co-selection)

Changes are Needed to the Methodology Described in the Concept Note

EPA has proposed a 3-step process by which it proposes to assess and mitigate AMR risk from pesticides in the U.S.

Risk Analysis Methodology

1) Resistance characterization
2) Risk assessment
    a. Release assessment
    b. Exposure assessment
    c. Risk conclusion
3) Risk management

In general, we agree with these three steps as they align well with how other agencies around the world are approaching this issue, but we are concerned with the failure of the Concept Note to include information about the medical importance of a drug in the risk assessment.

Resistance characterization is an appropriate first step and is consistent with what FDA labels as "Hazard Characterization" in Guidance #152 and what Codex Alimentarius labels as "Hazard

[14] https://www.sciencedirect.com/science/article/abs/pii/S0740002016304464?via%3Dihub
[15] https://www.cell.com/trends/microbiology/fulltext/S0966-842X(06)00051-5?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0966842X06000515%3Fshowall%3Dtrue
[16] https://www.sciencedirect.com/science/article/pii/S0048969722051567

Identification" in the Codex Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance.[17] The resistance characterization simply asks whether an AMR concern could possibly exist. This should not be limited to identifying shared mechanisms of resistance between the pesticide and a clinically relevant drug, but instead look at all scientific evidence that use of the pesticide can lead to increased resistance to a clinically relevant drug. Clinically relevant drugs are those that are medically important. At this point in the analysis, the determination is whether a resistance problem could occur – not the likelihood or the magnitude of the impact – which should be determined by the risk assessment.

If there is evidence of an AMR concern, then EPA should carry out a full risk assessment. In the Concept Note this is divided into separate release and exposure assessments that are integrated into a risk conclusion. Including separate release and exposure assessments is consistent with the FDA approach described in Guidance #152 but the Concept Note differs from the FDA approach in failing to include a consequence assessment as part of the risk assessment. This is a major failing of the methodology described in the Concept Note. Risk does not only include whether or not something happens but should also include the magnitude of the impact of what might happen. Resistance developing to a drug that is used to treat serious infections for which there are no or few alternatives is very different than resistance to a drug used to treat non-serious infection with multiple alternative treatments. As written, the Concept Note suggests that the medical importance of a drug should be considered only during resistance characterization[18] and that this information will not be included in the risk conclusion. This is a major flaw in the proposed method. The methodology should be modified to include a consequence assessment as part of the risk assessment which is integrated with the release and exposure assessments into the "risk conclusion."

The risk conclusion should clearly identify the qualitative level of risk (e.g. high, medium, or low) for pesticides identified as creating a risk of AMR. The risk conclusion then should be used to guide the risk management analysis, leading to a risk management decision with more protective mitigations for uses of pesticides that have been found to have a higher qualitative AMR risk.

Finally, EPA's risk analysis framework should include monitoring and review of foodborne AMR risk management measures. As recommended in the Codex Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance, risk analysis should be considered an iterative process that includes monitoring and review. We recommend the following adjusted methodology with additions in red.

Risk Analysis Methodology

1) Resistance characterization

[17] https://www.fao.org/fao-who-codexalimentarius/sh-proxy/jp/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXG%2B77-2011%252FCXG_077e.pdf

[18] EPA states: "Resistance characterization also considers the importance of a relevant drug (or any other drugs that could be impacted by the same resistance mechanism) to human or veterinary medicine and the strength of transmission pathways."

2) Risk assessment
    a. Release assessment
    b. Exposure assessment
    c. Consequence assessment
    d. Risk conclusion
3) Risk management
4) Monitoring and review

Risk Assessment Must Be Better Characterized to better determine whether a proposed pesticide use constitutes a potential risk to human or animal health due to AMR.

We recognize the tremendous complexity involved with assessing risk from AMR threats. First, AMR threats can manifest via exposure to resistant pathogens directly, or exposure to pesticide residues that can then select for resistance to microbes that exist on or within people. Further, there are different exposure scenarios that exist for different people. Farmworkers will likely have highest exposures overall since they directly apply antimicrobials and work in environments where the antimicrobials have been used; farmworkers and bystanders may face the most risk from inhalation/contact exposure; and young children will likely face the greatest risks via water/dietary intake. All of these exposure scenarios will likely result in very different exposure assessments for the same hazard.

We are concerned about the cumulative, synergistic, and additive health impacts on farmworkers from their exposure to antimicrobials over time. Specifically, we are concerned about health harms from antimicrobials modifying the farmworker microbiota, including leading to carriage and infection of resistant bacteria and fungi. In addition, we are concerned with antimicrobials bioaccumulating in farmworkers' bodies (cumulative impacts), interacting chemically with other pesticides to which farmworkers are exposed (synergistic impacts), and increasing the overall health harms to farmworkers when added to impacts from exposure to other pesticides (additive impacts).

Farmworkers can often be forced to work and live in unsanitary conditions and many don't have access to basic health care. These and many other compounding stressors must be incorporated into any risk analysis that purports to quantitatively or qualitatively estimate the likelihood that pesticide use can facilitate drug resistant infections in humans.

We feel that it is important for EPA to acknowledge the different exposure scenarios and the different populations EPA will assess risk to in the Concept Note to ensure that the ultimate framework is as strong and inclusive as possible.

Furthermore, to the extent that EPA is drawing on FDA Guidance #152 to assess different exposure scenarios, the Agency must account for the significant differences in the animal agriculture and plant agriculture contexts. In particular, while antibiotics are usually administrated orally or via injection to animals, there is much broader environmental exposure

associated with the spraying of pesticides on crops. These differences necessitate a very different way of conceptualizing and assessing risk.

Potential Risk Management Options Should be Identified and Explicitly Defined in the Proposed Framework Before Any Analysis is Conducted

Some of our groups submitted public comments regarding EPA's flawed proposal to approve the use of streptomycin on citrus crops. One of the most consequential things we observed in the AMR analysis EPA conducted for streptomycin was that the agency seemed ill-equipped to identify and implement appropriate safeguards needed to mitigate risk. It is important for EPA to identify a menu of mitigation options that are known to reduce exposure/risk from AMR. For instance, a low risk could result in one mitigation needed, medium risk would result in three, and high risk could result in five or more mitigations or ultimate cancellation of the pesticide. We reiterate the importance of identifying effective mitigations before any chemical-specific analysis is conducted to ensure that details of risk management are not developed *post hoc*. The FDA risk management approach described in Guidance #152 takes this approach and includes risk management recommendations that vary based on the identified level of risk with more restrictions recommended for uses leading to a greater antimicrobial risk. A similar approach should be used by EPA in the framework.

We strongly believe that risk mitigation measures must be a mandatory, enforceable statements on the pesticide label. Voluntary practices/measures do not provide effective mitigation. That said, even mandatory, enforceable labels often do not provide effective mitigation.[19] EPA must consider the reality that there is significant non-compliance with label language even when it is mandatory and enforceable. Without taking into consideration the reality of significant non-compliance with labels, EPA will overestimate the mitigation provided by pesticide labels—and thus underestimate the antimicrobial risks associated with the use of antibiotics as pesticides.

Such effective, mandatory mitigations could include:

1) Use cancellation or any other mechanism that would decrease use of the pesticide,
2) Prohibiting prophylactic or preventative use of a pesticide or requiring a certain crop infestation threshold to allow use of a pesticide.
3) Require monitoring for resistance along with thresholds for prohibiting further use once resistance has reached a certain point.
4) Conditional time-limited approval to address critical need while non-antimicrobial control methods are developed
5) Accelerated schedule for reassessment
6) Mandated use of IPM techniques for these pesticides to limit use
7) Setting industry-wide limits on use

[19] *See, e.g.*, Earthjustice Comments Opposing EPA's Proposed Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10, at 11-12 & nn. 64-66, https://www.regulations.gov/comment/EPA-HQ-OPP-2016-0067-0208.

To Determine if a Proposed Pesticide Use Constitutes a Potential Risk to Human or Animal Health Due to AMR, EPA Should Look at Target Organism Resistance For Insight Into Potential for Resistance Development in Human Health Pathogens

Consistent with a One Health approach, EPA's risk assessments should include an analysis of the documented resistance development in organisms that are targeted by the pesticide, including the prevalence of resistance to the pesticide in targeted populations, the mechanism(s) of action (if known) that resistance has developed, and the differential sensitivity to the pesticide from resistant and non-resistant populations.

While AMR development in plant pathogens in agriculture (target organisms) and AMR development in human pathogens are happening in two distinct pathogen populations, they are undeniably linked in terms of the processes by which they are facilitated. And with the potential for co-selection and horizontal gene transfer, AMR development in target organisms can potentially facilitate AMR development in human pathogens. Therefore, it is important for EPA to analyze these two processes together in a way that builds upon lessons learned and aligns with a One Health approach to inclusively analyze AMR threats to all organisms in the shared environment.

However, while human and plant pathogen development processes are linked, the mitigations necessary for each are not. The mitigations EPA is considering in the context of delaying target organism resistance in plant pathogens are not going to be adequate for reducing risk in the context of human health pathogens. While these two processes can inform one another, they will likely require very different risk mitigations to meet the safety standard under FIFRA.

EPA Must Collect Data to Monitor the Impact of Risk Management Decisions and Review those Data to Determine if Further Mitigations are Needed

One notable omission in the Concept Note is the lack of monitoring or data collection as part of EPA's strategy to reduce AMR in human pathogens. We acknowledge that high quality data in this context can take considerable time to develop and it's important that risk mitigations not be delayed waiting years for data to be collected. However, in order to confirm that risk mitigations are working and having the intended effect, monitoring, data collection, and review of actions are necessary. We want to be clear that requirements for monitoring or new studies are not risk mitigations themselves and cannot substitute for such mitigations. Study or monitoring requirements, however, can be one way to confirm the efficacy of risk management decisions. For instance, demonstrating that use of a pesticide has declined or that pesticide use has changed in a way that reduces the likelihood of AMR development. It is important that EPA conduct follow-up in a data-centric manner to ensure the efficacy of risk management decisions and inform any changes that need to be implemented.

Conclusion

We are currently in the midst of an AMR crisis. We must take any and all measures at our disposal to reduce this risk and ensure that antimicrobials continue to effectively fight life-threatening infections. EPA must therefore ensure that pesticide use whether antibacterial,

antifungal or other does not perpetuate the spread of AMR. We need a comprehensive and transparent approach consistent with One Health to assess the potential for crop pesticides to promote AMR in human and animal pathogens, and to include strong and effective mitigation measures as part of its risk analysis framework. We urge EPA and its federal partners to finalize this Concept Note and framework soon and begin doing individual assessments as soon as possible.

Respectfully submitted,

Center for Biological Diversity

Earthjustice

Food Animal Concerns Trust

Farmworker Association of Florida

Center for Food Safety

Health Care Without Harm

Center for Energy & Environmental Education, University of Northern Iowa

Antibiotic Resistance Action Center (ARAC) at the Milken Institute School of Public Health, George Washington University

Pesticide Action Network

Family Farm Defenders

Toxic Free North Carolina