August 15, 2024

Susan Jennings
Office of Pesticide Programs
Environmental Protection Agency
1201 Constitution Ave. NW
Washington, DC 20460-0001

Submitted via regulations.gov

Re: EPA-HQ-OPP-2023-0445-0085: DRAFT WHITEPAPER: Framework for Interagency Collaboration to Review Potential Antibacterial and Antifungal Resistance Risks Associated with Pesticide Use

Dear Ms. Jennings:

Established in 1933, CropLife America (CLA) represents the developers, manufacturers, formulators, and distributors of pesticides for agriculture and pest management in the United States. CLA's member companies produce, sell, and distribute nearly all the pesticide and biotechnology products used by American farmers. CLA represents the interests of its registrant member companies by, among other things, monitoring legislation, federal agency regulations and actions, and litigation that impact the pesticide industry and participating in such actions when appropriate.

RISE (Responsible Industry for a Sound Environment) is a national not-for-profit trade association representing more than 220 producers and suppliers of specialty pesticide and fertilizer products to both the professional and consumer markets. RISE member companies manufacture more than 90 percent of domestically produced specialty pesticides used in the United States, including a wide range of products used on lawns, gardens, sport fields, golf courses, and to protect public health.

CLA and RISE appreciate the opportunity to comment on the Environmental Protection Agency's (EPA or the Agency) DRAFT WHITEPAPER: Framework for Interagency Collaboration to Review Potential Antibacterial and Antifungal Resistance Risks Associated with Pesticide Use (the Draft Whitepaper). We also appreciate EPA extending the comment deadline by 15 days.

For clarity purposes, CLA and RISE are making the distinction between "antifungal/antibiotic" (clinical) and "fungicidal/bactericidal" (agricultural and non-agricultural) uses. Our comments focus on the scope of the Draft Whitepaper, the process for interagency coordination, stakeholder coordination, assessing resistance risks when making registration decisions under Federal Insecticide Fungicide and Rodenticide Act (FIFRA), mitigations and resistance management, and the research agenda to improve the risk assessment to determine the potential for fungicides and bactericides to contribute to the development of resistance in human-pathogenic bacteria or fungi (Appendix A).

Should you have any questions or comments, please feel free to contact us at: (202) 296-1585, mbasu@croplifeamerica.org, or kspotz@pestfacts.org.

Sincerely,

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Introduction

CLA and RISE support efforts by Federal agencies to address protecting public health, including ensuring that the impacts of pesticide products on antibacterial and antifungal resistance are minimal. We commend the efforts of EPA and other agencies, including Health and Human Services and United States Department of Agriculture (USDA), to work together on a One Health approach that includes developing a process to bring together scientists from different agencies to provide input on EPA's assessment of the potential for the spread of antimicrobial resistance in bacteria and fungi (AMR) from the registration of bactericidal and fungicidal pesticide products.

While CLA and RISE support efforts to ensure that agricultural and non-agricultural (e.g., lawns, forestry, golf courses) uses of fungicides and bactericides do not increase the potential for the spread of AMR and antifungal resistance (AFR), the Draft Whitepaper lacks sufficient specificity on the data required to evaluate the potential for AMR/AFR, how the assessment will be conducted, and the duration/resource needs for the assessment. The Draft Whitepaper contains many open-ended questions and approaches but does not outline a clear methodology that will be used for these assessments. CLA and RISE request that EPA provide a defined approach to the assessment and allow stakeholders to provide feedback on the approach.

We recommend the framework utilize clear and conceptually based scientific decision criteria and a logical path in applying the framework along the lines of our prior comment submission (CLA & RISE, 2023). This includes the incorporation of the hot-spot concept (or cold spot) to determine the potential for significant AMR selection. There are ongoing efforts in this area, and we encourage further collaboration with industry experts to discuss these efforts to develop a science-based risk assessment framework. This might include a first tier (after identification of the basic dual use of a fungicide class) screening for biological activity against target species, followed by determination of whether the ecology of the human pathogen in agricultural or non-agricultural settings intersects with pesticide application rates and residues capable of selective pressure. This will help to determine whether there is a potential hot spot. In parallel, the resistance selection potential must be driven by scientific evidence. Additional stewardship can include consideration of options for mitigations demonstrated to be effective against potential AMR selection (see comments below on mitigation practices and resistance management).

Antifungal and antibiotic chemistries used in human and veterinary medicine (dual uses), when administered responsibly, can co-exist with agricultural and non-agricultural uses of fungicides and bactericides. From a One Health perspective, it is critical that all sectors, including agriculture, human, and animal health all have equal input into decision-making that will benefit the health and well-being of the US population along with protecting the nation's critical infrastructure. While the development of new chemistries to treat human and animal bacterial and fungal diseases are clearly needed in the US and globally, it is critical not to overlook the vital importance of maintaining the existence of the fungicidal and bactericidal pesticide chemistries currently in use. Fungicides and bactericides are not only essential to agriculture to protect the food supply, but there are also several important applications of these chemistries for other use sites. For example, there are critical forestry applications of fungicides for the treatment of fungal infections in trees that can threaten the overall health of the nation's forests. This intervention also mitigates the risk of wildfires which not only increase carbon emissions but threaten human health with inhaled particulate matter, carbon monoxide exposure, and burns.

In agricultural settings, plant diseases caused by fungi or bacteria can result in significant crop losses, leading to a greater risk of food insecurity and negative economic impacts to US growers. These losses can amount to billions of dollars per year, causing farms to fail, further increasing the risk of food insecurity. Additionally, crop diseases caused by fungi present a significant human and animal health risk due to the production of carcinogenic, endocrine disrupting, and teratogenic mycotoxins. These risks can be mitigated by the application of herbicides to control weeds that increase crop stress and harbor fungi;

insecticides, which prevent the transmission of fungal pathogens carried by insects; and fungicides, which directly control the pathogen itself.

Other Factors Contributing to AMR

Many factors including overuse or misuse of antifungal agents and antibiotics in human and animal medicine are known to contribute to the development of resistance. Some examples include the chronic use of antifungals for immunocompromised patients and the inappropriate use of antibiotics to treat viral infections which disrupts the normal microbial flora and results in symptomatic fungal overgrowth requiring treatment. The use of antifungals to treat conditions not caused by fungi, inappropriate dosing and/or treatment durations, as well as the prophylactic use of antifungals to prevent fungal infections in low-risk patients may also contribute to the development of resistance (CDC, 2024). In addition, the pharmacological reliance on limited modes of action dependent mostly or entirely on triazole medications can contribute to increased selection pressure and resistance development.

Scope and Impact of the Draft Framework

The Draft Whitepaper describes what EPA plans to do to assess AMR risks but lacks the necessary specifics. To help support the regulated community's understanding of the scope and applicability of the overall framework and process, we have identified several areas for clarification. As stated previously, developing a clear problem formulation and conceptual model will help clarify the scope and the scenarios that would trigger AMR consideration as part of a risk assessment framework. That said, we appreciate that this document shall not be legally binding, and we support keeping the framework flexible to allow for evolving science and weight of evidence approaches. CLA and RISE additionally appreciate that an applicant can propose alternative processes to the final framework in any application to EPA.

Specific Active Ingredient Registration Scenarios That Require AMR Review

Based on the Draft Whitepaper, CLA and RISE understand that the AMR framework is intended to address new active ingredient (AI) registrations and registration review actions; however, EPA should clarify if the scope and applicability of this framework excludes other FIFRA actions. Given existing EPA guidelines for studies required for registration under FIFRA did not anticipate additional data requirements necessitated by this Draft Whitepaper, CLA and RISE request that EPA provide clarity on how the framework would be applied for AIs that represent dual use modes of action (MOA) that have already been submitted and pending registration at EPA.

Impact to Registration and Review Timelines

While the Draft Whitepaper outlines an approach for the development of an interagency workgroup (IWG), the process of identifying stakeholders of the IWG is not clear. We are concerned that incorporation of several stakeholders into the IWG may significantly impact and delay registration timelines, which could be detrimental for public health and the protection of the nation's food supply. In addition, the Agency should provide clarity on available resources to support this work so the IWG can function effectively and within the Pesticide Registration Improvement Act (PRIA) timelines given the resource constraints not only in EPA's Office of Pesticides Programs (OPP), but in other Federal agencies.

We request that EPA provide clarity to registrants regarding when a chemistry undergoing registration or registration review would be reviewed by the IWG and the timing associated with the assessment.

Azole and Antifungal Chemistries

CLA and RISE understand the strong focus on AFR and primarily azoles, given the potential human health impacts of cross-resistance. Yet, as noted in the Draft Whitepaper, significant research gaps exist that could take substantial time and resources to close, especially for assessing the development of AFR from fungicides. We appreciate that EPA acknowledges the significant information gaps on AFR; however, these unknowns should not lead to delays in the registration of products vital to maintaining the food system and important non-agricultural uses. Therefore, we request the Agency conduct a series of workshops with relevant experts and stakeholders to develop a science-based assessment framework.

Proposed Process for Interagency Coordination

CLA and RISE understand the intent and purpose of the IWG is to provide *ad hoc* expert review and input on the Agency's AMR reviews as requested. While the IWG allows for collaboration between many important agencies to provide expert opinions, CLA and RISE agree it is best for EPA to chair and lead any cooperative efforts. This will help to ensure that OPP can conduct its reviews under FIFRA, as experts from different agencies may not be familiar with OPP and FIFRA decision-making processes.

Additionally, we request the framework clearly define the roles and responsibilities of each agency in the IWG and how they will add to the science on the potential spread of AMR from pesticide use. There should also be clearly defined roles for how each of the agencies will contribute to the review of the draft risk assessments brought before the IWG. CLA and RISE request these defined roles be included in the memoranda of understanding (MOU) that EPA intends to develop with the federal partners as specified in the Draft Whitepaper.

Importantly, we request that in defining the process for interagency coordination, EPA allow stakeholders to provide input to the IWG through public meetings or a scientific advisory panel. This would enable stakeholders, including the user community and academia, to share their expertise and will facilitate increased communication within the regulated community.

The process should also include opportunities to collaborate in the form of a workshop, or series of workshops. These workshops could include the agencies and the innovator stakeholders (Ag and Pharma), who have a wide breadth of knowledge in this area. As described below, we have several research initiatives that are in progress, which will be valuable to share with the EPA, covering problem formulation and conceptual model development, as well as logical assessment frameworks and criteria to identify areas of concern.

Finally, a multi-agency workgroup has the potential to become overburdened and unfocused with the amount and scope of reviews needed. Considering this, we recommend the IWG develop a defined process that EPA can utilize on its own that is informed by scientific expertise from the other agencies. In this way, EPA could continue to work independently on pesticide risk assessments while still incorporating the scientific expertise and recommendations of the IWG.

Process for Stakeholder Coordination and Communication

CLA and RISE understand the draft framework's intent is to identify the potential for AMR across pharmaceutical and agrochemical chemistries. We encourage all stakeholders and agencies, to consider the benefits of agricultural and non-agricultural fungicides and antimicrobial products, as well as continued quantification, evaluation, and consideration of these benefits in final regulatory decisions. This requires stakeholder groups to understand information on classes of chemistry prior to the development of new chemistries for registration. Efficient and early communication will therefore be required to ensure the potential for AMR is fully addressed, and the candidate chemistry can be fully developed, without giving deference to one industry over the other. However, as noted in the Draft Whitepaper, there are significant challenges with this kind of data sharing and this data may not be readily available in many circumstances. We request a defined stakeholder coordination and communication process.

Assessing Resistance Risks and Making FIFRA Decisions

CLA and RISE acknowledge EPA's identification of information gaps, which we have further commented on in our comments on Appendix A. There are several areas where industry can collaborate with the agencies to address the highest priority outstanding research areas as highlighted in Appendix A. Many of these were mentioned in the CLA/RISE response to the 2023 Concept note (CLA & RISE, 2023). We believe that several of the noted areas of concern can be addressed through the development of a clear conceptual model and decision logic, and we encourage collaboration with industry, who have made extensive progress in this area. CLA and RISE would welcome an opportunity to engage with the Agency to share recommendations developed by the pesticide industry.

We request the Agency fully develop this framework before applying to FIFRA registration decisions. The framework should consider multiple sources of published information and lines of evidence to assess the likelihood of resistance selection among human pathogens present in the environment and their likely impact on the vulnerable portion of the human population.

We also support EPA's view that experience from assessing the resistance risk associated with the use of bactericidal pesticides is not easily adaptable to assessing the potential for resistance spread posed by fungicidal pesticides.

Mitigation Practices and Resistance Management

There are several practices recommended by registrants and adopted by growers/applicators which serve as mitigations/barriers towards AMR. Current agricultural practices and application methods in non-agricultural settings already incorporate resistance management practices. Pesticide label language already mitigates against the development of AMR potential. Examples of common label language include: rotating and/or mixtures of fungicide chemistries, application practices specified on the label to reduce pesticide runoff into bodies of water, spray drift mitigation methods to limit the potential of pesticide drift in the environment, using Personal Protective Equipment to limit dermal and inhalation exposure as specified on the label, following Pesticide Re-entry Intervals to limit exposure, cleaning/processing of harvested crops, using existing crop disease forecasting models to select the correct pesticide for the treatment of the specific pest, consulting with University Extension Agents on when to apply pesticides and when to rotate products to manage resistance potential, and using resistant varieties when available.

CLA and RISE advocate that pesticides should be used as part of an IPM program which involves consideration of information on the life cycles of pests and their interaction with the environment to develop an effective and environmentally sensitive approach to pest management with the least possible hazard to people, property, and the environment.

Research Agenda to Improve the Resistance Risk Assessment for the Use of Antifungal and Antibacterial Pesticides (Appendix A)

CLA and RISE appreciate the inclusion of the research agenda information in the appendix. The research conducted under this agenda should address questions whose answers lead to informed decisions. The objectives and criteria for funding research should not assume *a priori* that all pesticides can select resistant genotypes of human pathogens in the environment, or that they are the only agents capable of doing so.

EPA should work with the Centers for Disease Control and Prevention (CDC), Food and Drug Administration, and USDA to develop a list of priority fungi to help focus the research agenda. Creation of a subset of the listed human pathogens for consideration in connection with pesticide use must be based on knowledge of their respective ecologies (presence/reproduction rate) in agricultural settings. Here, *Aspergillus fumigatus* currently represents the single human pathogen for which sufficient evidence is available for selection of resistance in connection with (azole) pesticide use. The research should focus on specific MOAs (i.e., chemistries where there is current or anticipated "dual use" in clinical and agricultural settings).

Finally, pesticide registrants have extensive expertise in areas including cropping systems, fungal genetics, the epidemiology of resistance emergence and spread of AMR, etc. We welcome the opportunity to help support defining research priorities and the review of research proposals. Furthermore, we request the Agency clarify if the intent was to use "co-resistance" in this document, or "cross-resistance". In either case, the Agency needs to define these terms going forward.

Scope and Scale of Antifungal and Antibacterial Product Use in the Environment

The participating agencies of the IWG should already collectively have access to the data on antifungal and antibacterial product use in the environment. Persistence data should be available in regulatory documents already submitted by applicants. MOUs or inter-agency agreements can be used to facilitate initial data sharing. Comprehensive IWG and public review of the initial database should directly inform any future need for additional surveillance and where to prioritize further data collection. A targeted workshop (or series of workshops) with key stakeholders can help assess all information amassed along with its implications for pesticide use and risk assessment.

The agencies should specify how product use data will be used in risk management decisions. CLA and RISE caution against relating the volume of pesticide use to the risk of resistance selection. Each AI has different properties in terms of activity against human pathogens, but more importantly, selection of resistance may largely be restricted to certain "hotspot" settings (i.e. those in which a human pathogen is capable of extensive reproduction in the presence of concentrations of pesticide sufficiently high (as determined by application rates and the extent and localization of residues) to select for resistant genotypes.

Comprehensive Data on Baseline Levels of Resistant Fungi or Bacteria

Whole-genome sequencing (WGS) and multi-omics are the gold-standard approaches to elucidating microbial modes of action, and many advanced microscopy techniques are available to render 3D and confocal imagery that reveal docking characteristics. WGS is a comprehensive method for analyzing entire genomes that can allow for precise strain identification (and a possible method to distinguish between fungal strains found in the environment) while multi-omics approaches, such as metabolomics and transcriptomics, can inform the cascade from genotype to phenotype (and a possible tool for understanding antifungal MOA and downstream effects). While these are gold-standard approaches, their application to pesticide risk assessment is very new and thus any knowledge realized from this work is years away.

Considerable methodological information for characterizing resistance in fungal human pathogens is available in the scientific literature. Several research groups have applied such methodology to establishing baseline levels of resistance to medical antifungal triazoles in *A. fumigatus* populations (Chen et al., 2021; Chibunna Achilonu et al., 2023; Drakulovski et al., 2023; Hu & Chen, 2021; Jørgensen et al., 2021; Kortenbosch et al., 2024; Pintye et al., 2024; Verweij et al., 2022; Zhou et al., 2023, 2024).

Experience with *A. fumigatus* population screening indicates the importance of defining consistent cut-off concentrations for determining "resistance" to clinical standard products in *in vitro* tests such that temporal trends are determined on a reliable basis. The agencies should also consider how they define "resistance." Is this restricted to genetically stable mutations, or does it also include transient effects such as upregulation of cell efflux?

Consideration of climatic and geographic factors are important. Extensive European monitoring of environmental populations of *A. fumigatus* shows the proportion of resistant genotypes is highly variable spatially and temporally: the fact that the asexual (conidial) stage of the fungus is extremely mobile confounds attempts to pinpoint amplification of the resistant portion to specific locations. Sampling methodology should consider these challenges. Monitoring studies should include "control" locations to allow the potential impact of pesticide use to be compared with other factors relative to baselines.

Additional Data on Farming Practices That May Contribute to Development of Resistance

Managing and mitigating the risk of selection of resistance in human pathogens in connection with pesticide use will be most effective if it focuses on hotspots. The pesticide industry has defined the criteria for identifying a hotspot for selection and amplification of resistance in *A. fumigatus.* Some studies indicate fungicides are most likely to contribute to the selection and amplification of resistance in *A. fumigatus* if it is associated with waste piles or compost uses that support mass reproduction of the fungus (Doughty et al., 2021; Goertz et al., 2022).

CLA and RISE suggest that gaining a basic understanding of the points raised by the agency ("Data on how antifungal resistance occurs in the field or other environmental settings are lacking" and "Data are lacking to quantify the percentage of US fungal infections caused by antimicrobial-resistant fungi*")* should be obtained before moving forward with defining data requirements within an AMR framework.

Additional Data to Clarify the Relative Contributions of Pesticide Use

CLA and RISE also recognize the importance of understanding the factors determining the emergence and spread of resistant genotypes within a human pathogen population present in the environment. We therefore commissioned a study to further this understanding. Paveley et al., (2024) took *A. fumigatus* as a case study to define epidemiological considerations that should be generally useful when relating the ecology of human pathogens in the environment, including agricultural settings, to the risk of resistance selection through the use of pesticides.

Significant concentrations of human and veterinary drugs are known to be present in influent and effluent wastewater treatment facilities. Surface water is known to support populations of human pathogens (e.g., in biofilms). EPA and other agencies have already undertaken research initiatives to monitor environmental antimicrobial resistance and model the risk in surface water as part of the National Antimicrobial Resistance Monitoring System. This is an example of where the Agency will need to weigh the contribution of pesticides to selection of resistance in human pathogens against that of human and veterinary drugs in the environment.

Beyond pharmaceuticals, agricultural, and non-agricultural uses of pesticides, other environmental uses need to be considered which could have an impact on potential resistance development. Environmental uses of biocides and bactericides may need to be addressed differently than agricultural pesticides.

Additional Data to Assess the Populations That Might be Most Affected by Pesticide Exposure

CLA and RISE want to clarify that additional data is not needed in the present context regarding how human and/or animal populations are affected by exposure to pesticides*,* as this is adequately covered by the extensive and comprehensive regulatory package submitted by registrants under FIFRA. Rather, what is relevant is the human and animal exposure to the resistant portion of populations of human pathogens.

Gaining an understanding of the differing epidemiology of individual human pathogens in both the environment and the clinical setting will be vital to understanding the exposure of the vulnerable human sub-population to resistant genotypes. For *A. fumigatus*, the inhalation route is the most relevant; CLA and RISE are not aware of evidence to suggest that ingestion plays a significant role.

With this in mind, we see the need for a science-based regulatory approach to manage AMR/AFR risks which considers chemical MOA, hot/cold spots, IPM measures, and use of personal protective equipment in accordance with the pesticide label.

Conclusion

CLA and RISE member companies bring new innovative chemistries to market that are essential to protecting the nation's food supply and water bodies along with public spaces, lawns, and golf courses. We are currently experiencing significantly delayed product registration timelines. CLA and RISE are concerned that the interagency coordination under this framework could further slowdown product reviews and additionally delay registration timelines. Therefore, we request a defined plan for how the assessment for potential AMR can be efficiently applied to pesticide reviews so not to further delay bringing essential chemistries to market. Fundamentally, any necessary review with other agencies should occur concurrently while the data package and studies required for product registration are in review by the multiple offices within OPP.

Given the current budgetary environment, EPA is facing significant impacts to hiring, cuts to contracts, and delays to both PRIA and non-PRIA actions. Therefore, we are concerned about whether there are appropriate and sufficient resources available to EPA and possibly to the other agencies to responsibly steward this effort. Without proper management and administration of this program, it is likely to fail to produce results that can meaningfully inform regulatory decisions. Therefore, we request the Agency determine the resource needs for the IWG and work with stakeholders to allow them to conduct some of the assessment once the framework is finalized.

Finally, while we understand there are data gaps, especially in assessing the origin and spread of AFR, there are resistance management practices already specified on fungicide labels. Existing Best Management Practices, which include resistance management practices, and that are widely adopted by the grower and applicator community, should provide mitigation against AFR. Therefore, pesticide registration actions for AIs of concern should not be delayed for the development of a framework for assessing resistance potential. Applying an AFR framework with many data gaps is premature and could result in the loss of critical uses of fungicides that are essential to protecting the food supply and the environment (trees, forests, lawns, golf courses, green spaces) from the damage caused by fungal diseases. Additionally, CLA and RISE caution the Agency against widespread use rate reductions and cancelation of fungicide uses as a resistance management mitigation as this can have the unintended consequence of contributing to greater resistance of fungi that causes disease in fruit and vegetable commodities, ornamentals, turf in parks, commercial spaces, lawns and golf courses, trees, and forests.

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