Framework for Interagency Collaboration to Review Potential Antibacterial and Antifungal Resistance Risks Associated with Pesticide Use

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I. Purpose and Applicability

Purpose

The Office of Pesticide Programs of the Environmental Protection Agency (EPA) announces its Framework for expanding interagency collaboration to improve the communication and knowledge base within the federal family to fully consider potential adverse impact of pesticides on efficacy of human and animal antibacterial and antifungal drugs. The use of antifungal and antibacterial pesticides could potentially contribute to resistance in human and animal pathogens that may compromise the effectiveness of medically important[a] antibacterial and antifungal drugs. However, some of these pesticides may provide significant benefits to the health of agricultural crops and the U.S. food supply. There are also significant unknowns in our understanding of antimicrobial resistance risks associated with the use of pesticides in the environment. Additional information would help EPA refine the scientific evaluation for the regulation of these compounds.

This Framework outlines the process EPA will follow to collaborate with other federal agencies in assessing the potential risks of antimicrobial resistance developing from the use of antifungal and antibacterial pesticides. The Framework is designed to recognize the benefits of these pesticides to agriculture and minimize their impact on public and animal health, while considering the goals of the One Health approach. While developing this Framework, EPA has coordinated through an interagency process with the U.S. Department of Health and Human Services (through the Centers for Disease Control and Prevention [CDC] and the Food and Drug Administration [FDA]) and the U.S. Department of Agriculture (USDA), under the oversight of the White House Executive Office of the President. Each of the federal agencies is charged with protecting health in areas that are directly impacted by antimicrobial resistance resulting from pesticides or drug products used to protect humans, animals, or plants. This Framework explains that EPA is establishing a process to work with those other federal agencies to consider their expert input when EPA evaluates antibacterial and antifungal pesticide products that may adversely impact the efficacy of human or animal drugs.

As part of this process, EPA will collaborate with the other agencies, as appropriate, on scientific questions and uncertainties related to resistance and pesticides. Uncertainties surrounding the use of antibacterial and antifungal pesticides and their potential impact on human and animal health resulting from the development of resistant pathogens include how resistance develops, how it may migrate from the use site, and whether specific farming practices contribute to or mitigate the development of resistance in pathogenic bacteria or fungi. Appendix A provides a detailed outline of data that could help inform EPA's assessment of the potential for resistance from the use of antibacterial and antifungal pesticides and measures for mitigating that potential for resistance.

Applicability

EPA is issuing this Framework to provide information and clarification to pesticide applicants, growers, the public and animal health communities, and the public about EPA's process for considering resistance issues related to regulatory decisions on antibacterial and antifungal pesticides with other federal

[a] Defining "medically important" as it pertains to this framework will depend on a variety of factors, such as the drug's role in human medicine, the potential for cross resistance or co-resistance, and the availability of alternatives. An example of such a list for antimicrobial drugs is available from Appendix A of the Food and Drug Administration Guidance for Industry #152. Fungicides will be evaluated on a case-by-case basis. A list of antifungal drugs is contained in Appendix B.

agencies. While the requirements in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and EPA regulations are binding on EPA and applicants, this Framework is not binding on EPA personnel, pesticide registrants and applicants, or the public. EPA may depart from the Framework where circumstances warrant and without prior notice. Likewise, pesticide applicants may assert that the Framework is not applicable to a specific pesticide or decision. Registrants and applicants may also propose alternative processes to the final Framework in any application to EPA.

II. Background

Fungal and Bacterial Disease, Medications, Pesticides, and One Health

Antimicrobial resistance in bacteria and fungi is a top threat to the public's health and a priority across the globe. The CDC reports that there are nearly 3 million antimicrobial-resistant infections and more than 35,000 associated deaths in the U.S. each year.[1] Worldwide, antimicrobial resistance threatens progress in healthcare, food production, and ultimately life expectancy.[1] Most available data on antimicrobial-resistant infections focus on antimicrobial-resistant bacteria rather than fungi, but fungal diseases are also increasing worldwide. Increasing temperature caused by climate change could lead to an increase of fungi that can infect humans.[2] In the U.S., more than 75,000 hospitalizations and nearly 9 million outpatient visits occur every year for fungal diseases with direct medical costs estimated at $6.7 to $7.5 billion year.[3] Data are lacking to quantify the percentage of U.S. fungal infections caused by antimicrobial-resistant fungi.

According to USDA, plant diseases are also persistent threats to agricultural crops and global food security, having a significant impact on yields and quality. These diseases result in billions of dollars in economic losses and management inputs each year to crops, landscapes, and forests in the United States. Plant diseases reduce yields, lower product quality or shelf-life, decrease aesthetic or nutritional value, and may contaminate food and feed with toxic compounds. Plant diseases are caused by abiotic factors and biotic organisms including fungi, oomycetes, bacteria, viruses, viroids, and nematodes. Control of plant diseases is an essential component of food security and ensures an adequate supply of non-food crops for feed, fiber, energy, and horticultural uses. Effective control of plant diseases requires an understanding of the biology of these disease-causing agents.[4]

Some antibacterial and antifungal pesticides used in environmental settings belong to the same class as or share mechanisms of action with important antimicrobial drugs used in human and veterinary medicine. For bacterial pathogens, mobile genetic elements (i.e., plasmids) and bacteriophage can also form a reservoir of resistance genes that can cause pathogenic bacteria to become resistant via transference of genes. This gene transfer has caused antibacterial resistance to spread from commensal and environmental bacteria (those that are in the area when a pesticide is applied) to bacteria that are pathogens of animals and humans.[5] For fungal pathogens, recent evidence suggests that the use of some antifungal pesticides can lead to resistant organisms that pose a potential risk to human and animal health.[6] [7] [8] [9] [10] [11]

Federal Process

On September 26, 2023, EPA and the other federal agencies issued a document entitled "Concept Note: Soliciting Feedback from Stakeholders on the Structure of a Proposed Framework to Assess the Risk to the Effectiveness of Human and Animal Drugs Posed by Certain Antibacterial or Antifungal Pesticides." (88 FR 65998, September 26, 2023 (FRL-11370-01-OCSPP, docket no. EPA-HQ-OPP-2023-0445)The concept note was intended to be the first step in creating a process to improve assessments of potential risks to human and animal health where the use of certain pesticides could potentially result in antimicrobial resistance that compromises the effectiveness of medically important antibacterial and antifungal drugs. The concept note solicited stakeholder input on the proposed structure for the process

and potential solutions, research, and mitigation approaches to reduce the spread of resistance. The concept note posed several questions about how resistance occurs and is spread.

Over 5,200 comments were submitted to the docket from a diverse range of stakeholders ranging from researchers, public health organizations, growers, state and local governments, registrants, and public citizens. Most of these comments were part of a coordinated effort to promote stricter regulatory oversight, with an emphasis on One Health. Over 25 comments provided more detailed responses that discussed improving regulations, relying more on a One Health approach, the benefits of antifungal pesticides, importance of antifungal and antibacterial drugs to human and animal health, importance of antifungal and antibacterial pesticides to the food supply, uncertainties and data gaps, and mitigation strategies. Some of the comments also encouraged EPA to use scientific rigor and address the uncertainties and data gaps before moving forward with any regulatory changes.

Because very few comments directly responded to the specific charge questions asked by the concept paper, the agencies did not receive sufficient information to resolve the many scientific questions about assessing the potential risk of antifungal or antibacterial pesticides to adversely impact the efficacy of human or animal drugs.

On July 2, 2024, EPA published a document entitled, "DRAFT WHITEPAPER: Framework for Interagency Collaboration to Review Potential Antibacterial and Antifungal Resistance Risks Associated with Pesticide Use." (89 FR 54819, July 2, 2024 (FRL-11370-03-OCSPP, docket no. EPA-HQ-OPP-2023-0445) This draft Framework was developed to outline a process by which EPA would solicit advice from CDC, FDA, and USDA when considering the risks and benefits of a pesticide before making a regulatory decision that may impact the efficacy of an antibacterial or antifungal drug. The draft Framework also included a research agenda that outlined research needs to help EPA better understand and evaluate the potential resistance risks associated with antifungal and antibacterial pesticides. The draft Framework solicited stakeholder input on the proposed collaboration process.

Fourteen commenters responded to EPA's request for comment, coming from a diverse group of stakeholders ranging from researchers, industry groups, public health groups, veterinary groups, and one citizen. Many comments expressed concern about regulating with so many uncertainties, questioned the value of a qualitative assessment, stressed the importance of a transparent and open process, and discussed the content of the research agenda. Several commenters also requested clarification on the scope of the documents, which pesticides would undergo review by the proposed workgroup, registrant participation, and whether data requirements or EPA review times would change. EPA is issuing a response to comments document concurrently with this final Framework.

III. Regulatory Basis for Evaluating and Managing Risk of Resistance in Human Pathogens

Generally, a pesticide must be registered with EPA under FIFRA before it can be legally sold or distributed in the United States. During the registration process, EPA considers whether the pesticide will cause unreasonable adverse effects on people or the environment. Because the development of resistance in human or animal pathogens to antimicrobial drugs is considered an adverse effect of antibacterial or antifungal pesticides under FIFRA, the U.S. government is creating a structured and coordinated approach to assess and manage the risks of resistance developing in these pathogens of concern to human and animal health. Under FIFRA, EPA uses a different type of assessment to consider pest resistance that may develop in plant pathogens (or the target pest).

More specifically, FIFRA provides for federal regulation of pesticide distribution, sale, and use. FIFRA section 3(a) requires that pesticides be registered in order to be sold or distributed in the U.S., unless otherwise provided for in FIFRA. To be granted a registration, the applicant must show, among other things, that using the pesticide according to label specifications will not generally cause "unreasonable

adverse effects on the environment." FIFRA 2(bb) defines the term "unreasonable adverse effects on the environment" to mean: "(1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 408 of the Federal Food, Drug, and Cosmetic Act."

Under FIFRA, EPA can manage the potential risks of a pesticide, including the risk that an antibacterial or antifungal pesticide could contribute to the development of resistant pathogens, by ensuring that appropriate mitigations are incorporated into registration(s). Such mitigation sometimes includes measures to address human health and ecological risks, help prolong the lifespan of a pesticide, and reduce the opportunities for resistance to develop. Examples of mitigation measures to reduce resistance may include changing use patterns, adding personal protective equipment for users, or imposing buffer zones to limit off-site migration. In the past, EPA has determined that some of these mitigation measures are necessary to control the spread of resistance from the use of antibacterial pesticides to human or animal pathogens for certain products. Similar measures may help address fungicide resistance concerns, however, fungi present additional mitigation challenges. For example, *A. fumigatus* is a ubiquitous fungus that continuously disseminates spores into the environment.[12] These spores can be aerially transported off-site as they are continuously released at a high rate.[13] [14] They are also well suited to long-range transport and can remain airborne for very long periods.[15]

IV. Scope of Document

This Framework lays out EPA's process for interagency collaboration to support its assessments of the potential for resistance to occur in pathogenic bacteria or fungi for antibacterial or antifungal pesticides, respectively. EPA expects to rely on this framework for pesticides that share a mode of action or have the potential to cause cross-resistance or co-resistance with a medically important human or animal drug. Currently, this includes the azole pesticides (including those used in wood preservatives), some newer compounds that work by inhibiting the formation of dihydroorotate dehydrogenase in the targeted pest, and some antibacterial pesticides (currently kasugamycin, oxytetracycline, and streptomycin).

EPA will determine whether the collaboration envisioned under this Framework is appropriate for a particular pesticide registration action or registration review case by reviewing pesticide specific information (e.g., chemical class, spectrum, mechanism of activity) and bacterial or fungal resistance information submitted by the registrant, published in literature, and provided by federal partners. Examples of such resistance information could include information on existing resistance in the environment, bacteria or fungi that may develop resistance from the pesticide's use, and the identity of pathogens where resistance acquisition could impact the ability to treat disease in humans or animals.

V. Process for U.S. Government Interagency Coordination

To facilitate interagency collaboration, EPA, in collaboration with its interagency partners, is establishing a new workgroup, the Interagency Drug and Pesticide Resistance and Efficacy Workgroup (IDPREW). IDPREW's goal is to provide expert opinion, using a weight-of-evidence approach, on resistance issues involving antifungal or antibacterial pesticides, when requested by EPA, and potential interactions with medically important human or animal drugs. EPA will chair this workgroup. Initially, the workgroup will be comprised of several members with appropriate subject matter expertise from EPA, CDC, FDA, and USDA.

Determining a compound's potential to result in the development of antimicrobial resistance is complex. EPA will convene the IDPREW when there is available information that indicates a pesticide either

proposed for a new registration or undergoing registration review may impact the efficacy of a human or animal antibacterial or antifungal drug. EPA may also convene the workgroup for other reasons, such as if another agency requests a meeting or there are other regulatory decisions that would benefit from IDPREW consideration. Convening the IDPREW does not necessarily imply that a risk concern exists, but rather that there is some reason for inspecting the possibility. In most cases, EPA anticipates engaging with the IDPREW on antifungal or antibacterial pesticides with new modes of action or that share a mode of action with an existing human or animal drug. However, there may be cases where other types of pesticides could also trigger a review by the IDPREW, such as when there are questions about the pesticide's potential to impact the efficacy of a human or animal antibacterial or antifungal drug (e.g., an herbicide that shares a mode of action with an antibacterial or antifungal drug or a pesticide that could potentially cause co-resistance or cross-resistance). EPA plans to apply the Framework equally to all pesticides regulated by EPA's Office of Pesticide Programs, as appropriate, when there are questions about the pesticide's potential to impact the efficacy of a human or animal antibacterial or antifungal drug.

The IDPREW will provide its opinion about any characteristics of a compound that could lead to resistance in bacterial or fungal pathogens to human or animal drugs. The IDPREW's discussions and responses will likely vary in specificity from one pesticide to another because scientific information (as outlined in Appendix A) may be more available for some pesticides than for others. If EPA develops a risk assessment for the compound, it may also consult with the IDPREW to obtain feedback on the draft assessment, as appropriate.

IDPREW will also consider a drug's medical importance by evaluating factors such as the seriousness of the infections for which the drug is intended to treat and the availability of alternative treatments. For consideration of antibacterials, EPA expects the IDPREW to defer to FDA's Guidance for Industry #152[b] (GFI #152), as its Appendix A provides a ranking of antibacterial drugs according to their importance in human medicine. Oxytetracycline and streptomycin are antibacterial pesticides used in agriculture that are also used in human and animal drugs (kasugamycin is another antibacterial pesticide of concern). Examples of antifungal drugs that IDPREW may consider medically important include polyenes (e.g., amphotericin B), echinocandins (e.g., micafungin), and azoles (e.g., voriconazole, itraconazole). Appendix B of this Framework provides a list of antifungal drugs currently used for human or animal health, but the agencies have not yet determined whether each of those drugs is medically important. Neither of these lists is considered exhaustive.

Some information about drugs undergoing clinical trials is publicly available (e.g., through www.clinicaltrials.gov or published research articles). However, not all information that may be relevant for EPA's risk assessment, such as a drug's mechanism of action against the target microbes (and thus possibility of cross-resistance), will be accessible or publicly available for drugs undergoing clinical trials because of confidential business interests. EPA and the federal partners have signed a Memorandum of Understanding (MOU) to outline the terms and conditions for accessing, sharing, and using confidential information.

Each participating agency brings special knowledge and perspective into the IDPREW. CDC leads federal efforts for disease prevention and control in people, EPA is the U.S. regulatory authority on pesticide regulations, FDA is responsible for the regulation of both human and animal drugs, and USDA is responsible for protecting American agriculture and the American food supply. EPA expects that this collaborative interagency process will allow open and frank discussion between the agencies so that the

[b] EPA currently uses the 2003 version of GFI 152. FDA is in the process of updating this guidance and recently released a draft in 2022 for public comment. When FDA finalizes an updated version, EPA will consider transitioning to that version.

impact of pesticide use on resistance in human and animal pathogenic bacteria and fungi can be considered through a wider One Health lens.

EPA does not intend for the IDPREW to make a recommendation to grant or deny a specific pesticide application for registration. Such decisions are made by EPA under FIFRA. EPA does plan, however, to consider the extensive interdisciplinary expertise of the IDPREW and the information it supplies to EPA on the potential risks of a compound when making a FIFRA decision. EPA plans to post the IDPREW's findings to the docket for a decision with references to outside information and studies that were considered in the review, to the extent permitted by confidentiality restrictions.

VI. Assessing Resistance Risks and Making FIFRA Decisions

When registering pesticides, EPA considers the risks to human and animal health, including those due to resistant pathogenic bacteria or fungi impacting the efficacy of human or animal drugs. Direct risks from the pesticide itself (such as toxic effects or other risks associated with direct human exposure to the pesticide or environmental risks) are separately evaluated during EPA's pesticide evaluation process.

Infections attributed to resistant bacteria have long been a concern for public health; however, the public is less aware of infections attributed to resistant fungi. As an example, azole-resistant *A. fumigatus* has been found on every continent, except for Antarctica, with the highest number of reports from Europe. Resistant *A. fumigatus* infections have been found in people who have not been treated with azole antifungals, further suggesting that the resistance may be partially driven by environmental sources developed within humans being treated with azole drugs. A surveillance effort targeting molecular examination of pan-azole-resistant *A. fumigatus* isolates from patients in clinical settings in the USA, India, and the Netherlands found genetic markers within clinical *A. fumigatus* isolates for azole resistance that have been attributed resistance acquired in an environmental setting.[6]

For antibacterial pesticides, EPA has been currently applying a qualitative process to assess the resistance risks, adapted from FDA's GFI #152, which provides a qualitative risk assessment process to evaluate antimicrobial resistance risks to human health as a result of a drug used in food producing animals. EPA has adapted the process outlined in FDA's GFI #152 to evaluate risks to human health for antibacterial pesticides used on plants. This adaptation helps provide consistent public health goals for using antibacterial compounds outside of clinical medicine.

Fungi present distinctly different evaluation challenges from bacteria. Fungi and bacteria differ both biologically (e.g., how they reproduce) and behaviorally (e.g., how they move through the environment or infect humans and animals). While it has been shown that *A. fumigatus* can develop resistance to azole drugs (causing resistant infections in humans) from the use of azole compounds in the environment, there is a lack of comprehensive surveillance for azole-resistant *A. fumigatus* infections in the United States. Data on how antifungal resistance occurs in the field or other environmental settings are lacking, making the development of effective mitigation extremely difficult. Thus, while there are known mitigation options to limit resistance developing in plant pathogens (such as crop rotation and limiting application rates), mitigation options to reduce resistance in human and animal pathogens are extremely limited or poorly understood.

While existing research studies show the potential for resistance to develop in human pathogens from the use of antifungal use in the environment, studies demonstrating how this resistance develops are limited and the overall contribution of pesticides to resistance development is uncertain. Some studies indicate that antifungal pesticides have greater potential to contribute to *A. fumigatus* resistance development when associated with composting or waste piles,[16] which may serve as a reservoir and breeding ground for the development of resistance in *A. fumigatus* spores. Insight into how antifungal

resistance occurs in the field and the contribution of pesticide use or general agricultural practices to resistance development could help inform potential mitigation options to be considered in the future.

Accordingly, EPA's existing process for assessing the potential resistance risk associated with the use of antibacterial pesticides is not easily adaptable for assessing the potential for resistance posed by antifungal pesticides and their impact on human or animal antifungal drugs. The development of resistant pathogens in the environment is an active and growing area of research, and there are many variables that may impact if, how, when, and where resistance to antifungals may develop. The research agenda in Appendix A outlines a list of uncertainties that impacts EPA's confidence in assessing the resistance risks associated with antifungal pesticide use.

This Framework represents EPA's first step towards a broader approach to regulating antibacterial and antifungal pesticides and their potential to impact the efficacy of human and animal drugs. Moving forward, EPA will continue to work on advancing its regulatory process for assessing potential antibacterial and antifungal resistance risks associated with pesticide use. This includes addressing scientific questions associated with resistance development, pesticide use, and/or agricultural practices, such as those outlined in Appendix A. EPA may also consult with experts (e.g., through workshops or a Scientific Advisory Panel) to consider available information about the potential resistance risks posed by antibacterial and antifungal pesticides used in the environment. In addition, EPA will work with the IDPREW to gain a better understanding of any potential for antifungal pesticides to result in the development of resistance and impact on the medical importance of related drugs.

VII. Conclusions and Next Steps

This Framework describes EPA's plans for facilitating interagency collaboration about the potential for resistance to develop from the use of pesticides. As knowledge of the underlying mechanisms of resistance (how, when, and where pathogens develop resistance) from the use of pesticides becomes clearer, EPA intends to incorporate the findings into its regulatory processes and may update this Framework if appropriate. Together CDC, EPA, FDA, and USDA are committed to supporting and encouraging research, development, and application in this field, so that more robust and relevant scientific data become available to make better informed decisions. EPA and its partner agencies will continue to monitor the progress and developments, specifically in the environmental aspects of antibacterial and antifungal resistance. This information is critical to EPA's success in protecting the health of humans, animals, and the environment.

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

Some antibacterial and antifungal pesticides used in agriculture or other settings are similar to medically important antibacterial and antifungal drugs used in human and veterinary medicine.[17] Recent evidence suggests that the use of some pesticides can select for resistant organisms in the environment that pose a potential risk to human and animal health.[17] For example, certain triazole fungicides used in agriculture have the potential to select for strains of the environmental fungus *A. fumigatus* that are resistant to triazole drugs used in human and animal medicine (e.g., voriconazole).[6] As new pesticides and uses are proposed, the potential exists for some pesticides to select for pathogenic bacteria or fungi that are resistant to medically important antimicrobial drugs, including both FDA-approved drugs and those still undergoing late-stage clinical trials.[Error! Bookmark not defined. Error! Bookmark not defined.]

Substantial uncertainties exist regarding the risks to human and animal health posed by using pesticides that have the potential to select for resistance. This list highlights areas for development that, if filled, could help 1) inform assessments of the risk to the efficacy of human and animal antibacterial and antifungal drugs posed by certain antibacterial or antifungal pesticides and 2) clarify how to mitigate these risks.

- Additional data on the scope and scale of antifungal and antibacterial product use in the environment, including:
    - Ongoing surveillance to quantify current antibacterial and antifungal pesticide use (including information on volume used, how pesticides are applied, duration of persistence in the environment, etc.).
- U.S. studies have demonstrated the presence of azole-resistant *A. fumigatus* in various agricultural sites.[Error! Bookmark not defined. 11 Error! Bookmark not defined.] It would be useful to have data on baseline levels of resistant fungi or bacteria in environments where antibacterial and antifungal pesticides are used, including:
    - Development of standardized methods and implementation of studies to measure levels of resistant fungi or bacteria in environments where antibacterial and antifungal pesticides are used.
        - Standardized methods should include culture-based methods to enumerate/isolate organisms of concern, quantification of targeted resistance genes, and whole genome sequencing of isolates and whole environmental samples (i.e., metagenomics).
    - Assessment of any other factors associated with resistance (e.g., local geographic or climate-based characteristics)
        - Assessments should emphasize study designs which provide controls allowing for impacts of pesticide application rates (and other factors) compared to baseline levels.
- Additional data on the uses of antibacterial and antifungal practices that may contribute to development of resistance, including:
    - Determination of conditions that are most favorable to development of resistance.
    - The potential contribution of azole-containing wood preservatives to the development of resistance.
    - Analysis of crop groups or individual crops and the likelihood of resistance developing, given similar application types and rates of pesticide use.
    - Evaluation of farming practices that may inadvertently encourage selection for antimicrobial resistant fungi or bacteria (treatment/processing of leaf litter, on-site composting, etc.).

    - Analysis of the potential effects of pesticides on levels of antimicrobial resistance genes (ARGs) and mobile genetic elements (MGEs) in agricultural environments, including potential effects of pesticides on the frequency of horizontal transfer of ARGs and MGEs to pathogens.

- Additional data to clarify the relative contributions of pesticide use to the development of resistance compared with other potential drivers from other uses (such as medical or veterinary antibacterial or antifungal drugs), including:
    - Analysis of the mechanisms by which human or animal pathogenic bacteria and fungi and/or resistance genes spread through populations after becoming antimicrobial-resistant through selection by a pesticide's use.
    - Development of approaches and implementation of studies are needed to predict determinants of resistance using advanced molecular tools, such as whole genome sequencing, metagenomics, and modelling.
- Additional data to assess the human and/or animal populations that might be most affected by exposure to pesticides, including:
    - Studies to clarify how humans or animals encounter pathogens that may have developed resistance by exposure to these pesticides (e.g., through direct contact, inhalation, ingestion, healthcare-associated transmission, contamination of water supply, etc.).
    - Studies to evaluate the effect of antibacterial and antifungal pesticide-related resistance in populations that might be disproportionately affected (e.g., agricultural workers, persons handling compost, persons with immunocompromising conditions, persons living near treated fields, animals for food production, companion animals).
- Additional data on the use of integrated pest management principles[10] may help minimize the need for pesticide use and potentially help reduce risk of resistance. Opportunities to further minimize resistance risk include:
    - Development and optimization of additional crop disease forecasting systems to help growers predict when pesticide use is most needed.
    - Optimization of alternative crop disease management practices.
    - Innovative development of antibacterial and antifungal products specific for use in agriculture to preserve food security and agriculture industry.

Appendix B: List antifungal drugs used in human and/or animal health.

The following list contains systemic antifungal drugs that are currently used in human and animal healthcare. It is provided here only for reference and is not intended to be an exhaustive or complete list of antifungal drugs that may trigger additional resistance review.

Systemic Antifungal Drugs

Category	Antifungals
Allylamines	Terbinafine
Echinocandins	Anidulafungin Caspofungin Micafungin Rezafungin
Pyrimidine analog	Flucytosine
Triterpenoid	Ibrexafungerp
Griseofulvin	Griseofulvin
Imidazoles	Ketoconazole
Polyenes	Amphotericin B
Triazoles	Fluconazole Isavuconazole Itraconazole Oteseconazole Posaconazole Voriconazole

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