EPA Responses to Public Comments on FR 2024-14493

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 for EPA to solicit opinion from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) when making a regulatory decision involving a pesticide that may impact the efficacy of an antibacterial or antifungal drug. The draft Framework proposed formation of a new interagency workgroup, the Interagency Drug and Pesticide Resistance and Efficacy Workgroup (IDPREW) to provide EPA with an expert opinion from the other federal agencies. 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 an individual citizen. Many comments discussed concerns 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 to accommodate the IDPREW meetings. The commenters covered 42 comment areas and responses to these comments are below.

Along with the publication of this Response to Comments document, EPA is finalizing the Framework, which has been updated to address many of the suggestions made by commenters. Below is a detailed response to the issues raised by commenters responding to the draft Framework. For ease of review, this document is separated into 6 sections: Scope, Transparency and Public Engagement, Framework-specific, Risk Assessment, IDPREW Process, and Data Gaps and Research Agenda comments.

Scope

Comment #1: Details are lacking about exactly how a pesticide registration or review would trigger EPA to convene the IDPREW, and specifically what "evidence" is needed to begin the IDPREW process. If the EPA only convenes the IDPREW when there is already some predetermined level of evidence, it may be too late to best mitigate further resistance development by applying the expertise of the IDPREW members.

Response #1: EPA intends to convene the IDPREW when there is information about a pesticide either proposed for a new registration or undergoing registration review that may impact the efficacy of a human or animal antibacterial or antifungal drug. Such information may come in a variety of forms: published studies, outside requests substantiated with justification, or when the compound's characteristics imply that the pesticide may adversely impact the efficacy of human or animal drugs. 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 concern exists, rather that there is justification for inspecting the possibility. EPA has updated the document to clarify this point.

Comment #2: The scope of the Framework is unclear. While agricultural use pesticides constitute most of the pesticides registered by EPA's Office of Pesticide Programs (OPP), the Agency registers pesticides for use in a wide range of settings and applications. Please clarify which pesticides are covered by this Framework.

Response #2: If a pesticide shares a mode of action or has the potential to cause cross-resistance or co-resistance with a medically important human or animal drug, registrants should anticipate that they could be subject to this Framework. The Scope of Document section of the Framework (Section IV) states that the Framework "lays out EPA's intentions for a collaborative interagency process that would support EPA's assessments of potential resistance in pathogenic bacteria or fungi for antibacterial or antifungal pesticides. Examples include 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 (kasugamycin, oxytetracycline, and streptomycin). EPA has updated the document to clarify this issue.

Comment #3: EPA should provide clarity to registrants regarding when a pesticide undergoing registration or registration review would be reviewed by the IDPREW and the timing associated with the assessment.

Response #3: EPA plans to follow its standard regulatory processes, even where IDPREW is consulted on a submission. If registrants are concerned about whether IDPREW is meeting on a particular pesticide submission, then EPA suggests consulting with EPA at a pre-registration meeting or when the application is submitted to EPA.

Comment #4: There is limited evidence showing the development of cross resistance to medically important antibiotic and antifungal drugs from the use of antimicrobial pesticides. Our comments encouraged distinct approaches for antimicrobial and conventional pesticides in the consideration of an antimicrobial resistance framework for pesticides.

Response #4: EPA believes this commenter is using "antimicrobial pesticides" to mean those pesticides which are regulated by EPA's Antimicrobial Division. EPA's Antimicrobial Division regulates those pesticides which are used to destroy or suppress the growth of harmful microorganisms on inanimate objects and surfaces. At this time, EPA is not aware of any disinfectant product that could potentially cause resistance to a human or animal drug. However, EPA also believes the same approach—convening an interagency group of experts when available information indicates that a pesticide may lead to the development of resistance in human and animal pathogens to medically important drugs—is appropriate for all pesticides. EPA expects a meeting of the IDPREW to be helpful for the review of any pesticide that may have the potential to impact the efficacy of a human or animal antibacterial or antifungal drug. When EPA refers a pesticide to IDPREW, the workgroup will consider the unique properties and use patterns of the pesticide under discussion in its discussions, evaluations, and opinion.

Comment #5: EPA should clarify if the scope and applicability of this Framework excludes other FIFRA actions.

Response #5: EPA believes that the Framework clearly states that the process may apply to other actions. The Framework states, "… 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."

Comment #6: The terminology used to describe the Framework should allow stakeholders to understand which pesticides and approved (or unapproved) drugs are subject for inclusion in future resistance assessments and how that decision was made.

Response #6: If a pesticide shares a mode of action or has the potential to cause cross-resistance or co-resistance with a medically important human or animal drug, registrants should anticipate that they could be subject to this Framework.

Transparency and Public Engagement Comments

Comment #7: EPA should allow stakeholders to provide input to the IDPREW through public meetings or a scientific advisory panel (SAP).

Response #7: The IDPREW is a federal workgroup that will frequently discuss confidential information. The workgroup meetings cannot be made public without compromising confidentiality. As the Framework states, EPA intends to post any opinions provided by the IDPREW and considered by EPA in its pesticide decision making to the docket for specific pesticide actions. In its public communications, IDPREW is committed to leveraging all publicly available information to ensure the public has a meaningful opportunity to understand and engage with scientific concerns. EPA expects to follow its standard processes for regulatory decisions, including making supporting information used in its decision available to the public. Accordingly, the IDPREW opinion, with citations and supporting documentation, will be published to the docket, to the extent permitted by confidentiality restrictions. Stakeholders may submit comments to the docket as they would for other assessments or request a meeting with EPA to discuss their concerns. If an SAP is conducted in the future, it will be a public meeting according to standard EPA procedures.

Comment #8: The Agency should conduct a series of workshops with relevant experts and stakeholders to develop a science-based assessment Framework.

Response #8: EPA has requested public comment on this issue twice within the past year (with the concept paper and the draft Framework). EPA did not receive sufficient information to resolve or further the many scientific questions about assessing the potential risk of antifungal or antibacterial pesticides to adversely impact the efficacy of human or animal drugs. EPA is evaluating its next steps, including how a workshop or SAP may augment federal knowledge on this issue.

Comment #9: IDPREW should regularly engage with stakeholders across animal, plant, and human health arenas so that the expertise of these groups is utilized in IDPREW's decision-making process, and so the group has good visibility with the public. We recommend that the group's findings be published publicly to the extent feasible, as outlined in the Framework. While EPA's intention to post the IDPREW's findings to the docket is a good first step, adequate analysis and underlying studies and other information utilized by IDPREW should be posted along with any conclusions so that the public can understand and enhance IDPREW's proceedings.

Response #9: As mentioned in the Framework, EPA intends to post the IDPREW's findings to the docket, along with other scientific documents supporting the decision, to the extent permitted by confidentiality

restrictions. In these postings, EPA plans to post the IPDREW's analysis and references of studies that were considered in the opinion. The Framework has been updated accordingly.

Comment #10: The collaborating agencies should develop a plan for coordination with global partners, as has been done in other aspects of the federal response to antimicrobial resistance, recognizing that antimicrobial resistance knows no borders. This may be best accomplished through IDPREW, where representatives from multiple relevant federal agencies can engage with global partners. Having a set plan for regular global coordination will provide a stronger base for tackling antimicrobial resistance as not just a domestic, but a global, interconnected issue.

Response #10: EPA agrees that antibacterial and antifungal resistance is a global issue. EPA has an existing process to engage with regulatory agencies from other nations, which is expected to continue after formation of the IDPREW. Likewise, CDC, FDA, and USDA all regularly engage in international forums on the scientific aspects of the development, spread, and prevention of antimicrobial resistance.

Comment #11: Commenter requested that EPA provide a defined approach to the antimicrobial and antifungal assessment process and allow stakeholders to provide feedback on the approach.

Response #11: 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 may consult with experts (e.g., through workshops or an SAP) to consider available information about the potential resistance risks posed by antibacterial and antifungal pesticides used in the environment.

Comment #12: Prior to Framework implementation, EPA should understand the prevalence and the rates of resistance where a pesticide may be used.

Response #12: Prospective registrants are welcome to submit such information in support of their application(s). EPA's goal is to ensure there is sufficient information to reliably support registration decisions that are protective of human health and the environment, while avoiding the generation and evaluation of data that do not materially influence the scientific certainty of a regulatory decision. It is important to only require data that adequately inform regulatory decision making and thereby avoid unnecessary use of time and resources, data generation costs, and animal testing. EPA is working to address the scientific questions associated with resistance development and pesticide use and as mentioned above, may consult with experts to solicit input and feedback as EPA advances its regulatory process.

Comment #13: EPA should engage with a broad group of stakeholders, including industry, growers, researchers, and non-governmental organizations to understand costs associated with and impacts on timelines that the proposed Framework would create, as well as to understand resources required for conducting scientifically rigorous and appropriate studies to address research gaps and uncertainties. Workshops or other formats for bringing stakeholders together would be valuable for ensuring that the perspectives and insights of stakeholders and those of the participating federal agencies can be shared with respect to existing management practices, what registration actions the Framework will pertain to, implications for resistance management, and plans to close research gaps.

Response #13: EPA agrees that stakeholder input will be vital to developing a strong and robust Framework. The Agency is currently laying the foundation to continue improving and refining these risk assessments in the future and will consider these suggestions as it moves forward towards this goal.

Framework-specific Comments

Comment #14: The draft Framework neglects to mention GFI 152, Appendix A, is currently under review and has not been finalized.

Response #14: GFI 152 was first published in 2003 and then revised and issued as draft in 2022. EPA uses the 2003 version as its source when it created its adapted process because it is the most recent final document. When FDA finalizes a new document, EPA will consider transitioning to that version.

Comment #15: The Framework should provide a detailed definition of "medically important" drugs and an explanation of how the IDPREW will consider drugs that are in pre-approval stages at FDA.

Response #15: The term "medically important" refers to drugs used to treat microbial infections in humans.[1] For antibacterial compounds, EPA relies upon FDA's Guidance for Industry #152, Appendix A, for a list of medically important antibacterial drugs. Appendix B of the 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. Initially, these two lists can serve as a list of medical drugs of concern for resistance. However, EPA expects that this list(s) will evolve over time.

Comment #16: EPA should clarify if the intent was to use "co-resistance" or "cross-resistance" in this document.

Response #16: The intent of the Framework was to include both co-resistance and cross-resistance, as both may be relevant when considering potential antibacterial and antifungal resistance risks associated with pesticide use. Co-resistance refers to the simultaneous resistance of a bacterium or fungus to multiple antibacterial or antifungal agents that target the same cellular pathways or have similar mechanisms of action. Cross-resistance refers to the development of resistance in a bacterium or fungus against one antibacterial or antifungal agent that also confers resistance to another unrelated drug or drug class.

Comment #17: The definition of "resistance" in the document is unclear. Is this restricted to genetically stable mutations, or does it also include transient effects such as upregulation of cell efflux?

Response #17: For this Framework, antimicrobial resistance is defined as the ability of a bacterial or fungal pathogen to survive exposure to an antibacterial or antifungal drug that was previously effective at killing it. Antimicrobial resistance is not defined based on specific mechanisms of resistance, which could include genetically stable mutations or transient mutations (e.g., due to mechanisms such as polyploidy [production of extra copies of entire chromosomes] or those leading to constitutive upregulation of cell efflux), and therefore is not restricted to genetically stable mutations and does include transient effects.

Comment #18: EPA should provide further details regarding its desire to align the Framework with the goals of the CDC's O*ne Health* platform. *One Health* is an extremely comprehensive program that encompasses a wide array of topics and objectives.

[1] Defining "medically important" as it pertains to the 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.

Response #18: The implementation of the Framework uses an inherently One Health approach, as it considers the interconnectedness between human health, animal health, and the environment. The Framework does not refer to a CDC One Health "platform" because such a platform does not exist. CDC's efforts to combat antimicrobial resistance are implemented using a One Health approach.

Comment #19: The draft Framework is focused on azole-resistant *Aspergillus fumigatus*, which is a reasonable starting point given that the knowledge and understanding of it with respect to development of resistance and potential to cause disease in humans and animals is more developed than that of other fungal pathogens. However, other possible fungal pathogens with the potential to develop azole resistance and cause diseases exist within agricultural environments. Additional details on how the Framework can be updated for other fungal pathogens would be helpful.

Response #19: *Aspergillus fumigatus* is mentioned in the Framework as an example of a pathogen for which environmentally acquired resistance has led to resistance in a human drug. EPA does not intend to limit the application of this framework to a single pathogen, but rather expects to apply it more broadly to address resistance to other fungi and bacteria resulting from use of pesticides.

Risk Assessment Comments

Comment #20: The draft Framework states that EPA has used a qualitative process to assess the resistance risks, adapted from FDA's Guidance for Industry #152 (GFI #152). A qualitative risk approach determines the "likelihood" of an event occurring. Probability is a quantity and a quantitative approach to risk analysis determines risk based on a quantifiable number. The commenter believes the framework should use a science-based, quantitative approach to risk assessment.

Response #20: When assessing the risk of resistance to human and animal drugs developing from antibacterial and antifungal pesticides, current science is insufficient to support a framework for a quantitative assessment. EPA will continue to use a qualitative assessment until the science indicates another method would be more appropriate, at which point EPA will use its existing scientific process to develop the model and openly vet it through the appropriate scientific and regulatory channels.

Comment #21: Until there is clear research showing that real world relevant uses of antimicrobial pesticides could lead to the development of such cross resistance, a Framework to assess such risks is premature. Until the uncertainties are resolved or better understood, EPA must take a precautionary approach to approving and reregistering pesticides under FIFRA that have the potential to cause resistance in pathogens that decreases the efficacy of human or animal drugs.

Response #21: In most cases, a pesticide must be registered with EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) before it can be legally sold or distributed in the United States. EPA considers whether the pesticide could cause unreasonable adverse effects on the environment. FIFRA requires that registrants submit data that allows EPA to assess the risks and benefits of the pesticide. If use of an antibacterial or antifungal pesticide causes (or could cause) the development of resistance in human or animal pathogens to antimicrobial drugs, EPA considers that to be a potential risk of the pesticide under FIFRA. The Background section of the Framework (Section II) outlines scientific sources and findings indicating how recent evidence suggests environmental exposures to bacteria and fungi can lead to resistant organisms that pose a potential risk to human and animal health. EPA agrees (as discussed in the Framework and the accompanying Research Agenda (Appendix A)) that there are many uncertainties in the scientific database surrounding resistance and that additional data would help to further refine our scientific knowledge of the potential risk of antifungal and antibacterial

resistance developing from the use of pesticides. As such, EPA encourages registrants of such pesticides to submit all data relevant to this issue, and EPA plans to use a weight-of-evidence approach in evaluating potential for resistance to develop from the use of pesticides in the environment.

In addition to considering risks and potential risks of pesticides, EPA considers the benefits of the pesticide, which EPA acknowledges can be high for some antifungal and antibacterial pesticides. Both components are considered in EPA's determination of whether a pesticide can be registered under FIFRA.

Comment #22: We recommend the Framework utilize clear and conceptually based scientific decision criteria and a logical path in applying the Framework. This includes the incorporation of the hot-spot concept (or cold spot) to determine the potential for section of resistance.

Response #22: EPA agrees that the Framework should be a clear and science-based decision-making process. EPA has reviewed the hot-spot/cold-spot research and will consider these data when advancing its regulatory process to assess potential resistance risks associated with pesticide use, including future mitigation options. Additional research is needed, as outlined in Appendix A.

Comment #23: We recommend the IDPREW 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.

Response #23: EPA does not intend for the IDPREW to make a recommendation to grant or deny a specific application. EPA has the statutory obligation to make such decisions under FIFRA. However, EPA does plan to use the extensive interdisciplinary expertise of the IDPREW and the information it supplies to EPA in assessing the potential risks of a compound when making a FIFRA decision. The IDPREW is being established as a vehicle for EPA to solicit this support from its federal partners.

Comment #24: Although it may be tempting to rely upon theoretical mode of action or chemical class rationales in the absence of such empirical data, EPA should be mindful that a pesticide's mode of action and/or chemical class are not sufficient alone or in combination to substantiate a credible risk to resistance developing to medically important drugs.

Response #24: EPA is aware that determining a compound's potential to result in the development of antimicrobial resistance is a complex topic that requires the consideration of many factors. For this reason, the published whitepaper published earlier stated that, "EPA intends to convene the IDPREW when there is evidence that 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." This will allow ample opportunity to take a broad look at the available data.

Comment #25: EPA and federal partners must ensure that mitigation measures to limit resistance that protect workers and do not disproportionately burden them.

Response #25: EPA agrees that worker protection must not be overly burdensome when protecting workers from resistance or any other pesticide risk.

Comment #26: It is problematic for EPA to continue to rely on PPE use by farmworkers as a risk mitigation method, particularly in hot and/or humid environments. Not only does that approach put the burden on the farmworker, not the employer, to protect themselves from exposures, it also ignores common use issues and practices associated with PPE.

Response #26: EPA appreciates this comment, however, the framework is focused on how EPA will gather input on potential risks and not particular mitigation decisions for particular pesticides. This comment is beyond the scope of this document, but as noted above, EPA agrees that worker protection should not be overly burdensome.

Comment #27: EPA must address the risk of pesticide drift causing selection pressure on off-field bacteria and fungi, the risk of farmworker exposure to resistant bacteria and fungi upon reentering a treated field, and all other pathways and factors that may increase exposure to farmworkers.

Response #27: EPA agrees that all known pathways of exposure are worthy of investigation.

Comment #28: These products degrade quickly once they are introduced into the environment. Consequently, the Agency should review the available field data and based on the weight-of-evidence, confirm that the use of these antibiotic pesticides is understood and not a significant concern regarding the potential to facilitate antibiotic resistance in humans or animals.

Response #28: Pesticides present different ranges of risks and benefits. Based on our review of data mentioned in the Framework, EPA does not agree that all antibiotic pesticides can be cleared of any potential to lead to resistance in human or animal pathogen.

Comment #29: It appears that the only potential area where there may be an opportunity for the fungicide and pool of fungi to interact under conditions that may impact resistance in humans and food animals involves the composting of treated material. Composting generates a high-temperature environment. The presence of fungicide residues coupled with the potential presence of the pool of thermophilic fungi of concern in a relatively warm environment may present a potential pathway of concern regarding antimicrobial resistance in human pathogens. If so, then labeling mitigation restrictions precluding the composting of treated commodities in large quantities may be warranted.

Response #29: EPA acknowledges that composting may be one potential source of resistant fungi, however further research is needed to understand how the resistance develops and is spread. EPA appreciates this comment and will consider it as we move forward to advance our assessment of the risks for resistance.

<u>IDPREW Process Comments</u>

Comment #30: Details are lacking about exactly how a pesticide registration or review would trigger EPA to convene the IDPREW, and specifically what "evidence" is needed to begin the IDPREW process.

Response #30: If registrants are concerned about whether a specific antibacterial or antifungal pesticide may trigger IDPREW, then EPA suggests consulting with EPA at a pre-registration meeting or after the application has been submitted to EPA.

Comment #31: The process of how the IDPREW will operate is not clear. How will stakeholders be chosen to participate, how will agencies staff the IDPREW, how often will it convene, etc. The Agency should provide clarity on available resources to support this work so the IDPREW 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, but in other Federal agencies.

Response #31: The IDPREW will be comprised of federal employees from each of the participating agencies (CDC, EPA, FDA, USDA) and these employees will be designated by management for each of the

respective agencies. The Memorandum of Understanding (MOU) will contain additional details; however, frequency and content of meetings will vary with the individual characteristics of the pesticides under review. As the Framework indicates, the IDPREW will not include outside stakeholders to ensure confidentiality of information shared between agencies. Although EPA does not anticipate that the resources needed to convene the IDPREW itself will significantly impact the statutory timeframes in PRIA, resistance is complex and regulatory issues may arise that impact the timetable for review of particular pesticide products. If delays do occur, EPA will inform the registrants using existing channels of communication.

Comment #32: 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 resistance 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.

Response #32: We have updated the Framework to include this information.

Comment #33: No specific information has been provided regarding what will be in the MOU, how the MOU will practically function, how the MOU will influence Framework implementation (e.g., timing, process, etc.), whether EPA intends for the MOU to be legally binding, or whether government authorities that are not included in the MOU and/or non-governmental organizations (NGO) and other stakeholders (e.g., pesticide registrants, drug developers, growers, etc.).

Response #33: The MOU is being released concurrently with the final Framework. The MOU is intended to lay the groundwork for cooperation between the federal agencies and ensure confidentiality of data sharing among the agencies. The MOU is not a legally binding document. EPA does not solicit external comments on the content of MOUs.

Data Gaps and Research Agenda Comments

Comment #34: We support addressing *Candida auris* as a threat in the Framework and believe it should be included as a research priority and as a priority for surveillance.

Response #34: The Framework establishes a process for EPA to consider information and expertise of other federal agencies when it evaluates antibacterial and antifungal pesticide products that may adversely impact the efficacy of human or animal drugs. Determining priorities for research and surveillance of specific pathogens is beyond the scope of this Framework.

Comment #35: Registrants need to be informed of the type of data that will be required during the IDPREW process.

Response #35: EPA does not anticipate requiring any additional data to support the IDPREW process at this time. It will rely upon other data submitted to support registration as well as data published in valid, peer-reviewed sources. The registrants will be expected, as they are with other risks assessed by EPA, to discuss resistance issues and respond to questions about their specific application. If additional data needs are identified, EPA will inform the registrant.

Comment #36: EPA must clarify how to fill the significant data gaps identified in the draft Framework related to antifungal and antibacterial pesticides.

Response #36: Appendix A is a list of research that could be conducted to resolve some of the uncertainties in evaluating pesticides for potential risks of development of antimicrobial resistance that impact that efficacy of human and animal antibacterial and antifungal drugs. It is not intended as an exhaustive list, nor is it considered "must have" data for risk assessments. Some of the uncertainties listed in Appendix A could help inform potential mitigation. EPA does not have the resources or the mandate to conduct extensive research studies; this list is published to guide others who may have the resources and the ability to conduct research and help reduce the uncertainties for evaluating the potential risks of resistance developing that could impact the efficacy of human drugs from antibacterial and antifungal pesticides used in the environment. Consultation through workshops and a SAP could help inform how to fill scientific data gaps using currently available or future research.

Comment #37: 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.

Response #37: This is beyond the scope of this document but will be taken into consideration as EPA works towards addressing the scientific uncertainties.

Comment #38: IDPREW should publish a Research Agenda either directly or via the EPA following the example given in Appendix A of the Framework. This will provide robust evidence to support research groups in their efforts to secure funding to address knowledge gaps.

Response #38: While EPA conceptually agrees with this comment, the Agency does not have the resources to further examine or publish additional information on the research agenda.

Comment #39: Appendix A does not explicitly address the ecology of antimicrobial resistance genes (ARGs) and mobile genetic elements (MGEs) associated with the spread of ARGs via horizontal gene transfer in the agricultural environment. These should be added to the research agenda and include the effects of resistance causing pesticides on the level of ARGs and MGEs and the frequency of horizontal transfer of such ARGs to pathogens.

Response #39: We have added the following wording to the research agenda (under "Additional data are needed on farming practices that may contribute to development of resistance"): *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.*

Comment #40: EPA should utilize its authorities under FIFRA to fill the critical data gaps pertaining to resistance issues and pesticides.

Response #40: EPA may consider using its data-call in authority in its future discussions on resistance.

Comment #41: The Interagency Drug and Pesticide Resistance and Efficacy Workgroup (IDPREW) should prioritize addressing other aspects of antifungal resistance because of pesticide use. Areas for prioritization include: the limited routine susceptibility testing in human and veterinary medicine, lack of surveillance for antifungal resistance emergence, less established breakpoints and clinical data to interpret fungal resistance testing, and the need for greater awareness of the increased risk of resistant fungal infections in immunocompromised patients.

Response #41: The IDPREW is being developed to provide a process for EPA to consult with federal experts to ensure that EPA assessments use current, cutting-edge science when considering risks from antibacterial and antifungal pesticides to the efficacy of human and animal drugs. While the above areas

mentioned in the comment may be appropriate for future work, they are beyond the scope of this Framework.

Comment #42: The collaborating agencies should develop and implement a clear, well-resourced plan to collect and publicly report data on antimicrobial use in pesticides and plant health and for related resistance, similar to surveillance and data collection activities that have been established for human and animal health. This will help evaluate the risk for emerging One Health threats and make this information publicly available for stakeholders to use in research and policy making. There is already sufficient data to indicate that antimicrobial use in any setting contributes to the development of resistance, so data gaps are not a valid reason to delay efforts to address antimicrobial use in pesticides.

Response #42: Surveillance is an ongoing discussion and issue in both the national and international forums; however, it is beyond the scope of this Framework.