Consideration of Disinfection Hierarchy Concepts in the Registration of Antimicrobial Products

This White Paper is designed to serve as a starting point for discussions with stakeholders on the expanded use of a "disinfection hierarchy" as a tool in the evaluation of efficacy of antimicrobial pesticides. The paper explains how the United States Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) currently uses such a hierarchy in its regulation of antimicrobial pesticides and explores the key scientific issues that may arise from expanding this use.

In its simplest form, the disinfection hierarchy concept describes the descending order of susceptibility of classes of microorganisms to antimicrobial chemicals. The susceptibility order could be between or within classes of microorganisms. This concept and some examples of how it has been used (and could be used) are further explained in the following sections.

OPP is considering expanding its use of the disinfection hierarchy concept and is seeking input on options that can be supported by current science and the scientific issues to consider as factors in its use. OPP's main goals are to: (1) provide more expeditious guidance to health care officials and the public on the most effective type of registered antimicrobial products on the market to use against an emerging pathogen and (2) increase the efficiency of and lower resources associated with registering antimicrobial pesticides while maintaining a high level of public health protection.

EPA will hold a "Disinfection Hierarchy Stakeholder Workshop" on October 7, 2015, in Arlington, VA. The workshop will be focused on the scientific merits of the hierarchy as the basis for EPA regulatory decisions. The workshop will provide a forum for stakeholders to discuss: (a) the current science on which disinfection hierarchy concepts are based, (b) scientific issues that may present challenges for its use in registering antimicrobial pesticide products, and (c) ideas on how to address these issues.

Description of Disinfection Hierarchy Concepts

A disinfection hierarchy describes the descending order of susceptibility of various classes of microorganisms to antimicrobial chemicals. Figure 1 illustrates the microbiological order from least susceptible class of microorganisms (i.e., hardest to disinfect) to the most susceptible class of microorganisms (the easiest to disinfect). [1-4] Application of the disinfection concept can occur vertically (between classes) or horizontally (within classes)."

The Spaulding classification system sets the stage for the use of disinfection hierarchy concepts. In an effort to prevent healthcare-associated infections (HAIs), E. H. Spaulding developed a classification system based on tiers of risk (Figure 2).[5-7] Spaulding's system is based on a patient's risk of infection from contact with a contaminated surface, and the notion that there are varying degrees of antimicrobial activity that are dependent upon the method or agent used to treat surfaces. Although not a taxonomic hierarchy, inherent in

Spaulding's classification system, and what has become apparent to microbiologists over time, is the awareness that different classes of microorganisms exhibit different degrees of susceptibility to antimicrobial chemicals due to biochemical and biophysical characteristics of the organism.

Spaulding's classification system has been adopted by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) to guide disinfection policies. CDC has established categories for recommended processing activity levels based on a hierarchy: sterilization, high-level disinfection, intermediate-level disinfection, low-level disinfection, and non-critical environmental surfaces.[8] The FDA used the hierarchy to develop criteria to support efficacy claims for the defined CDC processing levels. For example, a sterilant must destroy all forms of microbial life, including bacterial spores as demonstrated by a specific required sporicidal test method. In another example, high-level disinfectants are defined as those that destroy all mycobacteria, all ordinary vegetative bacteria, fungi, small or non-lipid viruses, medium-sized or lipid-containing viruses, and some bacterial spores. FDA recommends a specific testing regime to demonstrate this level of efficacy.[9]

The FDA approach is an example of a vertical application of disinfection hierarchy concepts. According to the Klein-Deforest Scheme[10], viruses are divided into three categories based on differences in their outer structure, which determines their susceptibility to disinfectants. The Klein Deforest Scheme is an example a horizontal application of disinfection hierarchy concepts.

EPA's Current Regulatory Practice and Use of Hierarchy Concepts

Antimicrobial pesticides are substances or mixtures of substances used to eliminate or suppress the growth of harmful microorganisms (e.g., bacteria, viruses, fungi, etc.) on inanimate objects and surfaces. The EPA regulates pesticides, including products with antimicrobial activity, under the statutory authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). In the United States, antimicrobial products bearing claims for control of microorganisms on inanimate surfaces that are infectious to humans are considered to have "public health claims." In EPA's view, users of antimicrobial pesticides with public health claims will expect the products to perform as claimed, and there could be health consequences if they do not perform as expected. Therefore, under FIFRA, EPA requires the registrant of an antimicrobial product with a public health claim to submit efficacy data in support of the product's registration. OPP has developed guidelines for registrants to use in the testing of pesticides and toxic substances, and the development of test data for submission to the Agency. Group B — Antimicrobial Efficacy Test Guidelines Series 810.2000-2700 (http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series810.htm) are for antimicrobial pesticides.

To some extent, EPA already regulates antimicrobial pesticides with public health claims using disinfection hierarchy concepts. EPA has established three main antimicrobial product categories based on the degree or level of antimicrobial activity. The three categories are sterilant, disinfectant and sanitizer (Appendix A, Table 1). The disinfectant category is further subdivided into three categories of product claim: limited spectrum

disinfectant, broad spectrum disinfectant and hospital disinfectant. For each category, EPA has established testing standards necessary to provide assurance of efficacy, including the test organism(s) a product must be evaluated against. A product that demonstrates efficacy within a particular category may convey label claims for the category itself (e.g., "hospital disinfectant") and claims for the specific microorganisms required to be tested for that particular category (e.g., "*Pseudomonas aeruginosa*"). For claims against additional bacteria and viruses, EPA requires registrants to submit efficacy data for each individual microbe.

As an example of EPA's current regulatory practice and the general use of disinfection hierarchy concepts – if a company wishes to register Product A, a hospital disinfectant and tuberculocidal product that is also for use against *Listeria*, EPA requires efficacy testing to be conducted against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (for the hospital claim), as well as *Mycobacterium bovis* BCG (for the claim as a tuberculocidal product) and *Listeria* (for the specific label claim against *Listeria)*. In this example, testing is required against four test organisms to obtain the desired label claims. Any additional claims against other microorganisms, such as a virus, would require additional efficacy data. The addition of forty or more microorganisms to a product label is not uncommon.

Considering the large number of viruses and bacteria that present a public health concern, the current approach poses a growing regulatory challenge for EPA. The requirement for extensive testing may also present biosafety issues, logistical (e.g., organism availability, culturing, etc.) and laboratory accessibility concerns for industry, as well as potential user confusion. In short, the current approach consumes considerable time and resources for both industry and government, which can ultimately impact public health protection.

In addition to EPA's general use of the disinfection hierarchy for establishing antimicrobial categories for product registration, EPA has also successfully employed disinfection hierarchy concepts for allowing the use of registered products for treating surfaces contaminated with emerging viral pathogens. EPA's emerging pathogen guidance is focused specifically on viral pathogens* such as SARS coronavirus (SARS-CoV), influenza A (H1N1) virus, and Ebola virus for which, at the time of an outbreak, there were no registered products available with such claims.[11] In these situations, EPA used a hierarchal approach to recommend products with a presumed level of efficacy with higher or equal effectiveness against the emerging pathogen. For example, an EPA-registered hospital disinfectant with a label claim for use against a non-enveloped virus (e.g., norovirus, rotavirus, adenovirus, poliovirus, etc.) was deemed appropriate for disinfection of surfaces contaminated with Ebola virus.

* For this effort, the Agency defines, "emerging pathogen" as any infectious organism capable of causing disease in humans (whether through natural person-to-person transmission or through zoonotic transmission) that has newly reached either endemic, epidemic, or pandemic levels. This includes reappearing pathogens (old and new) that have established identification by the CDC.

EPA's Consideration of Expanding the Use of Disinfection Hierarchy Concepts for Registering Antimicrobial Pesticides

Why does EPA want to explore a broader use of a disinfection hierarchy in registering antimicrobial public health pesticide products? EPA's experience in applying the hierarchy concept to emerging pathogens, as well as the demonstrated rapidity in terms of public health protection, are significant factors in EPA's consideration of whether or not a broadly-applied disinfection hierarchy could be used routinely for antimicrobial product registration. A broader use of the hierarchy would allow more expeditious responses to emerging infectious diseases and thus, better public health protection. Moreover, broader reliance on the hierarchy would streamline the approach to registering antimicrobial pesticides, saving time and resources and would provide a practical approach for users. Decontamination of environmental surfaces is conducted without knowledge of the specific organism(s) present; furthermore, contaminated surfaces commonly have an array of unknown microbes. Thus, having an antimicrobial product approved for a use site to disinfect against broad classes of microorganisms provides a more simplified product selection process.

If proven reliable, there are multiple ways a disinfection hierarchy could be used to streamline product registration. In one option (in the broadest sense), disinfection hierarchy concepts could be fully applied vertically down all microorganism classes from least to most susceptible to disinfection. As an example, consider Product A from the previous section where efficacy testing was required for four microbes. Following the microbial hierarchy vertically, the efficacy data for *Mycobacterium* would be sufficient to support claims against the other three microbes (*Staphylococcus, Pseudomonas,* and *Listeria*) because they fall below *Mycobacterium* on the microbial hierarchy, and would be considered more susceptible to disinfection under the same use conditions.

In another, more limited option, EPA could define the efficacy standards for each category of product and identify the representative organism(s) necessary to evaluate the efficacy of an antimicrobial product against a class of microorganisms. Under this approach, if an antimicrobial pesticide displays acceptable efficacy against the defined representative microbe(s) for a class, EPA could conclude that it was also effective against other microbes in the class that are deemed more susceptible. This could eliminate the need to test against or, alternatively, to submit data for each individual organism.

Then again, EPA may decide that the hierarchy is more suited for a narrower use. For example, EPA could decide to use the hierarchy to support reduced data for certain types of claims (e.g., only enveloped viruses) or for certain product types (e.g., only sanitizers), or for certain uses (e.g., only residential use products). An example of a partial application of disinfection hierarchy concepts would be to have the applicant tests against all microorganisms on the label but only submit data to EPA on select, representative microorganisms.

EPA is assessing the scientific merits of the hierarchy as the basis for EPA regulatory decisions, with respect to several considerations. These include:

- Variables impacting efficacy: There are a number of factors that may influence the efficacy of antimicrobial products and the use of the hierarchy.
    - Physical parameters – pH, temperature, soil load, surface type, etc.,
    - Chemical parameters – active ingredient(s), formulation, surfactants, etc.,
    - Suitable test methodologies, including method variability

Representative microorganisms: It is common practice to use certain species of microbes to represent other microorganisms in a class that have similar properties or characteristics. Is this a scientifically valid approach for assessing the efficacy of antimicrobial products? [12] If so, assessing what microorganism characteristics are relevant for susceptibility is critical. For example, it is common to consider whether a virus is enveloped or non-enveloped. It may also be important to consider genetic makeup and viral shape.

EPA is seeking input on the following questions:

1. What are the potential variables that might affect the hierarchical order and, thus, the stability of the hierarchy and reliability of representative organisms under different conditions?
    - Which variables have the greatest impact on the stability of the hierarchy? To what degree does this vary between classes of microorganisms?
        - Physical parameters (pH, temperature, soil load, surface type, etc.)
        - Chemical parameters (active ingredient(s), formulation, surfactants, etc.)
        - Method variability
    - What options might be considered for addressing variables that have an impact on the stability of the hierarchy?

2. What is the scientific basis for and what are the limitations of the selection of representative microorganisms within a class of microorganisms?
    - What are the relevant characteristics of the microorganisms to consider in determining the most appropriate test organisms to represent all pathogenic organisms within a class?
    - In what classes does the science suggest that more than one representative organism may be needed? For which other class(es) of microorganisms is there sufficient information to identify a representative microorganism that reliably meets all the relevant characteristics?

3. In what ways is the application of disinfection hierarchy concepts supported by current science?
    - Given current science, in what ways and/or for what classes of microorganisms can disinfection hierarchy concepts be applied sooner rather than later?
    - What are important limitations based on current science?

4. What would be useful next steps?
    - What data and/or scientific studies could be completed relatively quickly, which could support additional application of the disinfection hierarchy – and in what ways?
    - What other scientific or policy considerations should EPA take into account in considering expanded use of the disinfection hierarchy for regulatory purposes?

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Appendix A

Table 1. Summary of EPA Testing Guidance for Antimicrobial Claims on Hard, Non-porous Environmental Surfaces

Base Claim	Base Test Organisms	Allowed Additional Claims	Additional Test Organisms
Sterilants			
Sterilants/Sporicides	Spores of *Bacillus subtilis* [American Type Culture Collection (ATCC) 19659] and *Clostridium sporogenes* (ATCC 3584)	Additional high-risk spores	Spores of *Clostridium difficile* (ATCC 43598)* or *Bacillus anthracis*
Disinfectants			
Hospital or healthcare disinfectant	*Staphylococcus aureus* (ATCC 6538) and *Pseudomonas aeruginosa* (ATCC 15442)	Additional bacteria	Bacteria claimed on the label
		Fungicidal disinfectant	*Trichophyton mentagrophytes* (ATCC 9533), then other fungi claimed on the label
		Virucidal disinfectant	Virus claimed on the label or approved surrogate
		Tuberculocidal disinfectant	*Mycobacterium bovis* BCG
Broad-spectrum disinfectant	*Staphylococcus aureus* (ATCC 6538) and *Salmonella enterica* (ATCC 10708)	Additional bacteria	Bacteria claimed on the label
		Fungicidal disinfectant	*Trichophyton mentagrophytes* (ATCC 9533), then other fungi claimed on the label
		Virucidal disinfectant	Virus claimed on the label or approved surrogate
		Tuberculocidal disinfectant	*Mycobacterium bovis* BCG
Limited spectrum disinfectant	*Staphylococcus aureus* (ATCC 6538) or *Salmonella enterica* (ATCC 10708)	Additional bacteria	Bacteria claimed on the label
Sanitizers			
Non-food contact surface sanitizer	*Staphylococcus aureus* (ATCC 6538) and [*Klebsiella pneumoniae* (ATCC 4352) or *Enterobacter aerogenes* (ATCC 13048)]	Additional bacteria	Bacteria claimed on the label
Food contact surface sanitizer (halide products)	*Salmonella enterica* (ATCC 6539) or *Staphylococcus aureus* (ATCC 6538)	Additional bacteria	Bacteria claimed on the label
Food contact surface sanitizer (non-halide products)	*Escherichia coli* (ATCC 11229) and *Staphylococcus aureus* (ATCC 6538)	Additional bacteria	Bacteria claimed on the label

*Claims against spores of *Clostridium difficile* are only allowed on products labeled for hospital use.

Figure 1. Microbiological disinfection hierarchy. Examples of microorganisms in each category are provided.

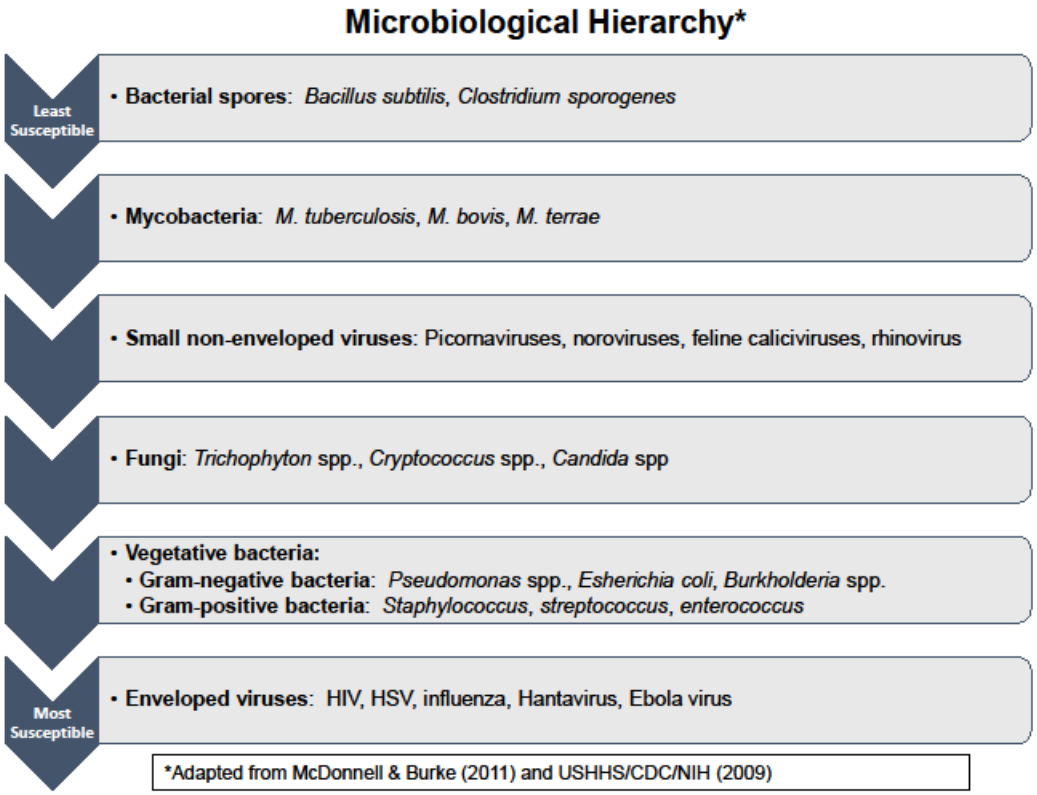

Figure 2. Spaulding (FDA/CDC) disinfection hierarchy.