PROPOSED 158W SIGNIFICANTLY EXPANDS ANTIMICROBIAL DATA REQUIREMENTS BEYOND THOSE HISTORICALLY OR CURRENTLY IMPOSED

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The Antimicrobials Division has stated that the proposed 40 CFR Part 158, Subpart W, codifies existing practices with regard to data requirement decisions for registration of antimicrobial pesticides and does not expand those requirements. To test this assertion, the ACC Biocides Panel compared the data requirements for a theoretical indoor food use pattern under "conventional 158" (as revised in 2008 and found in 40 CFR 158, Subparts F through O) against those for a theoretical antimicrobial indirect indoor food-contact use using the latest draft version of 158W available to the ACC Biocides Panel, the "April 2011 158W draft" (April 2011 draft). The information needs described under conventional 158 are the requirements currently applicable to antimicrobial registration. Specifically, the theoretical use in this exercise was selected to be indoor use of a disinfectant on surfaces in an environment where there is indirect contact with food/feed bound for human or livestock consumption (e.g., treatment of surfaces in livestock premises in between broods). This comparison was performed for a subset of the data requirements: non-target organisms, non-target plant protection, environmental fate, residue chemistry, and toxicology.

This limited analysis indicates that there are approximately 60 instances in which the April 2011 158W draft potentially exceeds the data requirements for an indoor pesticide, as defined in the 2008-revised conventional 158 data tables. The additional cost to a single applicant seeking to register an antimicrobial product for <u>all</u> of these "new" data requirements ranges from $7,331,814 – 18,161,280. These cost estimates were derived by examining both EPA study cost data (which, except where otherwise noted in the below tables, is usually the smaller dollar amount) and the study cost figures prepared by NERA Economic Consulting (which were, in most cases, the higher dollar amount). NERA's analysis was included in the comments previously submitted to the draft 158W rule docket (EPA-HQ-OPP-2008-0110) in 2008. It is recognized that each registrant's cost will differ and that EPA may not require the registrant to conduct all of the studies identified in the following tables.[1] It should finally be noted that estimates of study costs are based on those costs typical of testing conventional pesticides

[1] According to the Agency response to comments as provided in the April 2011 draft rule, the average cost per registration action for a new active ingredient is $1 – 5 million while the average additional cost of new data needed for registration review action an an indirect food use antimicrobial pesticide is $284,000 (and "high exposure" uses would be expected to cost $588,000). The figures presented in this analysis are well in excess of these estimated costs presented by EPA. There is a high likelihood that indoor uses of antimicrobials shall also be designated as "food use," thus incurring the costs of generating the required additional data (i.e. food handling, food processing studies, etc.) as well as the costs of supporting information (such as developing new analytical methodologies to support a new food-use tolerance, dietary studies and developing the petition itself). The costs of these supporting data can be substantial and are not captured in the cost estimates presented in the tables herein.

and, in many cases, are not fully reflective of extra costs incurred by modifications to existing guidelines (such as the potential additional cost of radiolabeling) and developing, validating and obtaining necessary prior Agency approval of entirely new protocols (i.e. nature of residue on surfaces, monitoring of representative US waters).

More specifically, these results break down as follows:

- Conventional 158 data requirements for Non-Target Organisms (40 CFR 158, Subpart G; §158.630), Indoor use, were compared against the All Other Uses category in the April 2011 draft. There were 16 instances of expanded data requirements, including new "higher tier" testing requirements. If a registrant were expected to conduct each of these 16 studies, it would entail an additional cost of $2,471,029 – 4,988,163. It should be noted that three tests comprise the bulk of this cost: fish full life cycle (850.1500), bioaccumulation, biomagnification and bioavailability to aquatic organisms (850.1710, 850.1730, 850.1850), and mesocosm studies/field testing for aquatic organisms (850.1950). Lastly, study costs for chronic toxicity to aquatic sediment-dwelling organisms are uncertain, as there is no protocol available on which to reliably base cost estimates (the high end cost listed is $240,000, which could be surpassed depending on study duration, number of samples needed, number of taxa needed, etc.). There is no dependable way to determine at this stage which registrations will need to meet which data requirements, thus violating the key principle of predictability and avoiding vagueness.

- Conventional 158 data requirements for Non-Target Plant Protection (40 CFR 158, Subpart G; §158.660) were compared against the All Other Uses category in the April 2011 draft. Non-Target Plant Protection is not a requirement for conventional indoor use pesticides under Part 158; therefore, all 6 requirements in this category are treated as new requirements. If a registrant were expected to conduct each of these 6 studies, it would entail an additional cost of $451,893 – 1,749,250.

- Conventional 158 data requirements for Environmental Fate (40 CFR 158, Subpart N; §158.1300), Indoor use, were compared against All Other Uses category in the April 2011 draft. There are 14 instances of expanded data requirements, including brand new data requirements for Toxicity and Fate in Wastewater Streams and expanded application of the soil and aquatic Metabolism studies (835.4100, 835.4200, 835.4300, and 835.4400). If a registrant were expected to conduct each of these 14 studies, it would entail an additional cost of $932,236 – 2,838,338. It should be noted that costs for some of these studies are likely to rise should radiolabeling be required (see 835.3110 below). No study costs were identified for biodegradability in discharged wastewater (835.3280) and, most importantly, there is no available protocol on which to reliably base an estimate for "monitoring of representative US waters." This is notable as the range reported below is quite variable and costs well in excess of $1 million dollars are feasible given study duration, number of samples needed, etc.

- Conventional 158 data requirements for Residue Chemistry (40 CFR 158, Subpart O; §158.1410), Indoor Food use, were compared against All Other Uses in the April 2011 draft. There were 14

instances of expanded data requirements, including new requirements for surface residue studies and expanded application of "higher tier" residue studies. If a registrant were expected to conduct each of these 14 studies, it would entail an additional cost of $1,633,083 – 5,170,000. It must be stressed that the estimated costs for Residue Chemistry data are the least reliable of all the areas examined as part of this analysis. In fact, no study costs were identified for established requirements 860.1550, 860.1560, and 860.1650. EPA has not yet developed Guidelines for nature of residue on surfaces and migration testing assays and thus there is little information upon which to base a reliable cost estimate.

- Conventional 158 data requirements for Toxicology (40 CFR 158, Subpart F; §158.500) were compared against both the Direct and Indirect Food Uses in the April 2011 draft. There were 9 instances of expanded data requirements, including additional triggers for subchronic and chronic animal studies. If a registrant were expected to conduct each of these 9 studies, it would entail an additional cost of $1,843,573 – 3,415,529.

The specific instances of increased data requirements are set forth on the attached tables. It seems likely to the Panel that analysis of additional requirements associated with other uses of antimicrobials (but not considered in this analysis) also will demonstrate increases in required data. The increases appear to be largely related to the following factors:

Food Use Designations: The April 2011 draft expands the use patterns that EPA would regulate as "food" use. For example, use of disinfectants (previously defined as products with directions for use mandating a potable water rinse and regulated as non-food use) now would be regulated as a food-contact use. Surfaces not previously considered food contact (e.g., stove tops, microwave and refrigerator interiors) would now be regulated as food-contact surfaces. This regulatory change in food use designations will substantially expand toxicology and residue chemistry data requirements not only for large numbers of active ingredients but also for a thousand or more inert ingredients.

Residue Chemistry Data Requirements: If the April 2011 draft 158W data requirements were issued as is, the residue chemistry data requirements would be greatly expanded for antimicrobial pesticides. While the April 2011 draft stated that the requirements are tiered, such tiering is not reflected in either the data table or the notes explaining the conditions for requiring data. The data requirements for this section are organized (and triggered) by designations of potential exposure ("high" or "low") rather than through any tiered system of data collection, such as the toxicology data requirements where results of acute studies predicate the need for longer-term studies. Given this, it is unclear why antimicrobial pesticides applied indoors should have more extensive data requirements when compared to conventional pesticides with similar use patterns. For example, indoor use of conventional pesticides does not trigger data requirements for potable water (835.1400), fish (835.1400) and irrigated crops (860.1400), yet these studies are conditionally required for indoor use of antimicrobials and represent a potential additional aggregate testing cost of at least $ 900,000. Further, EPA has asserted that it will require residue chemistry studies for uses regulated by FDA as indirect food additives pursuant to FFDCA section 409.

Non-Target Organisms and Environmental Fate Data Requirements: The April 2011 draft imposes significantly expanded non-target organism/plant and environmental fate data requirements for all antimicrobial uses. EPA appears to have assumed that some indoor uses, such as material preservative uses where the antimicrobial is incorporated in the matrix of a consumer good, have greater potential for environmental exposure relative to a conventional pesticide applied indoors. For example, acute ecotoxicity data are required for all indoor uses in the April 2011 draft, whereas "indoor use of liquid formulations" is exempt from these studies under the conventional 158 requirements. Moreover, none of "higher tier" chronic ecotoxicity assays are required of conventional pesticides when used indoors, yet these are all conditionally required of antimicrobials. Similarly, the entire category of non-target plant data requirements (along with the Toxicity and Fate in Wastewater Streams assays found under the Environmental Fate requirements) have *never* been required for *any* indoor use to date, as these are, by and large, all brand new assays.

Toxicology Data Requirements: The April 2011 draft imposes expanded toxicology data requirements for indoor use patterns. For example, if co-formulants are expected to enhance toxicity of the active ingredient or act to increase dermal absorption, then additional dermal animal data are needed. If the inhalation or dermal routes of exposure are found to be the "primary route," then the relevant subchronic data is needed. Overall, it appears as if exposure considerations for triggering subchronic and chronic animal studies have been dropped, such as references to "levels of concern" in the conventional 158 data tables. Finally, it must be noted that the Agency has redefined what constitutes a domestic animal for the purpose of triggering the Companion Animal Safety requirement, which is notable given the very large cost of this single study.

In summary, the Panel believes that EPA's position that the April 2011 draft data requirements do not represent an expansion over current requirements is at odds with this comparison. This has resulted in a flawed economic analysis because the economic impact of these increases in data requirements have not been estimated or assessed. The April 2011 draft should be re-proposed with an accurate, up-to-date economic analysis, providing stakeholders with the opportunity to comment on these extensive changes and their economic impacts.

Comparison of the Non-Target Organism data requirements for Conventional 158 (Indoor Use) and the April 2011 draft of 158W (All Other Uses)

The layout of the table below reflects the most current version of the 158W data requirements (the most current version available to the Panel is the April 2011 draft) for determining toxicity to non-target organisms from "All Other Uses" of antimicrobial pesticides, which would include indoor uses. In the rule proposed in 2008, this category was referred to as "Low Exposure" (see 73 FR 59382; October 8, 2008). In the April 2011 draft, these requirements are separated into tiers: there are three required "Tier One" tests as well as two required "Higher Tier" tests. The three required Tier One tests determine the species that is most sensitive to acute toxicity and the required Higher Tier tests are generally performed with this organism; however, there are triggers for Higher Tier testing based on physicochemical properties and exposure potential as well. Note that certain acute studies may need to

be done for both the technical-grade active ingredient and the end product, with the end product testing done as part of the Higher Tier testing. All Higher Tier testing requirements are new requirements for indoor uses of antimicrobial pesticides.

Please note the following abbreviations are used throughout the table:

- R = required study (non-conditional);
- CR = conditionally required (conditions under which the study must be performed are written into the Test Notes that accompany the data tables);
- NR = not required (conditions under which this study is not required are written into the Test Notes that accompany the data tables); and
- NOT IN TABLE (these studies are not found in conventional 158 data tables).

Where appropriate, the "triggers" for conditionally required studies are included in the data tables, to gauge clarity of the conditions under which the study is required and to show changes across conventional 158 and the April 2011 draft.

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Tier One Testing			

[2] As listed in 40 CFR 158.

[3] Use patterns for Non-target Organism Data Requirements (as listed in the April 2011 158W draft) are Industrial Processes and Water Systems, Antifoulant Coatings and Paints, Wood Preservatives, Aquatic Areas, and "All Other Uses."

[4] Except where otherwise noted, the range of costs for individual studies is defined at the lower end by EPA estimates and at the higher end by estimates provided to EPA by the ACC Biocides Panel as part of its comments on the draft 158 rule of October 8, 2008. See Docket EPA-HQ-OPP-2008-0110, comments dated April 6, 2009. Specifically, higher end estimates of study costs were derived by NERA Economic Consulting presented in Appendix A of these comments.

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Acute avian oral toxicity (850.2100)	**CR** (not required for indoor use of liquid formulations; not generally required for EPs that are gas, highly volatile liquid, highly reactive solid, or highly corrosive; required of MUP to support indoor EP)	**R** (required "Tier One" study for one avian species)	Low: $ 10,100 High: $ 11,700
Acute freshwater invertebrate toxicity (850.1010)	**CR** (not required for indoor use of liquid formulations; not generally required for EPs that are gas, highly volatile liquid, highly reactive solid, or highly corrosive; required of MUP to support indoor EP; EP testing required if introduced directly into the environment, if MEEC exceeds a level of concern or if EP component enhances TGAI toxicity or is toxic to aquatic organisms)	**R** (required "Tier One" study for one freshwater aquatic invertebrate)	Low: $ 17,000 High: $ 19,500

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Acute freshwater fish toxicity (850.1075)	**CR** (not required for indoor use of liquid formulations; not generally required for EPs that are gas, highly volatile liquid, highly reactive solid, or highly corrosive; required of MUP to support indoor EP; EP testing required if introduced directly into the environment, if MEEC exceeds a level of concern or if EP component enhances TGAI toxicity or is toxic to aquatic organisms)	**R** (required "Tier One" study for either one coldwater or warmwater species)	Low: $ 19,064 High: $ 19,500
Higher Tier Testing			
Avian dietary toxicity (850.2200)	**NR**	**CR** (dependent on results of acute avian oral "or its principal transformation products are likely to occur in avian feed items")	Low: $ 6,480 High: $ 19,500 (cost based on 1 species; however, test may be required in multiple species)

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Avian reproduction (850.2300)	**NR**	**CR** (required for one avian species; required "if birds may be subjected to repeat or continuous exposure to pesticide or any of its transformation products, especially preceding or during breeding" or if residues or principal transformation products are likely to occur in avian feed items or if residues accumulated in plant or animal tissues; or if any other information indicates reproduction may be adversely affected by product use)	Low: $ 168,250 High: $ 195,000 (cost based on 1 species; however, test may be required in multiple species)
Acute freshwater invertebrate toxicity (850.1010)	**NR**	**CR** ("Tier Two " study required on 1 freshwater aquatic invertebrate; TEP testing required based on selected deterministic or probabilistic modeling results or if EP component expected to enhance toxicity)	Low: $ 17,000 High: $ 19,500

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Acute freshwater fish toxicity (850.1075)	**NR**	**CR** ("Tier Two" study required on either one coldwater or warmwater species; TEP testing required based on selected deterministic or probabilistic modeling results or if EP component expected to enhance toxicity)	Low: $ 19,064 High: $ 19,500
Acute marine and estuarine toxicity (850.1025, 850.1045, 850.1055, 850.1075)	**NR**	**CR** (required on a mollusk, fish and invertebrates species; TEP testing required based on selected deterministic or probabilistic modeling results or if EP component expected to enhance toxicity; required "if pesticide residues and/or transformation products are likely to enter estuarine/marine environment")	Low: $ 19,064 x 3 = $ 57,192 High: $ 20,800 x 3 = $ 62,400 (cost is per species; however, three species are required)
Fish early life stage (850.1400)	**NR**	**R** (required "Tier Two" study to be conducted on most sensitive organism as identified in required "tier 1" acute toxicity tests)	Low: $ 37,279 High: $ 71,500

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Aquatic invertebrate life cycle (850.1300, 850.1350)	**NR**	**R** (required "Tier Two" study to be conducted on most sensitive organism as identified in required "tier 1" acute toxicity tests)	Low: $ 45,500 High: $ 118,063 (note that NERA cost is the low value and EPA cost in high value)
Fish life cycle (850.1500)	**NR**	**CR** (required if "product is expected to enter environment in significant concentrations because of its expected use or mobility patterns"; required if EP "applied directly to water or is expected to be transported to water from the intended use site" based on deterministic or probabilistic modeling outcome or "if studies of other organisms indicate that the reproductive physiology of fish may be affected")	Low: $ 390,000 High: $ 512,5000 (note that NERA cost is the low value and EPA cost in high value)
Aquatic organisms, bioavailability, biomagnification, toxicity tests (850.1710, 850.1730, 850.1850)	**NR**	**CR** (required based on selected chemical characteristic data or hydrolytic half-life and if there are potential exposures to fish and other non-target organisms)	Low: $ 325,000 x 3 = $ 975,000 High: $ 325,000 x 3 = $ 975,000 (note that there are three separate tests)

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Simulated or actual field testing for aquatic organisms (850.1950)	**NR**	**CR** (New methods must be confirmed by independent laboratory; protocols must be approved by EPA; required if "intended use pattern, physical/chemical properties and environmental fate characteristics of the antimicrobial indicate significant potential exposure" and results of acute and chronic organism testing)	Low: $ 600,000 High: $ 2,600,000
Whole sediment acute freshwater invertebrates (850.1735)	**NR**	**CR** (Protocols must be approved by EPA; required based on selected chemical characteristic data or half-life in sediment)	Low: $ 20,250 High: $ 52,500
Whole sediment acute marine invertebrates (850.1740)	**NR**	**CR** (Protocols must be approved by EPA; required based on selected chemical characteristic data or half-life in sediment; required if "product is expected to enter environment in significant concentrations... because of its expected use or mobility patterns")	Low: $ 37,500 High: $ 52,000

Non-Target Organism Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[2]**	**April 2011 158W Draft All Other Uses[3]**	**Range of Study Costs[4]**
Whole sediment chronic invertebrates freshwater and marine (none)	**NR**	**CR** (Protocols must be approved by EPA; required based on selected chemical characteristic data or half-life in sediment; required if "product is expected to enter environment in significant concentrations... because of its expected use or mobility patterns")	Low: $ 51,350 High: $ 240,000 (note there is no draft Test Guideline upon which to reliably estimate cost; estimate provided by registrant and assumes testing done on 3 organisms)

Comparison of the Non-Target Plant Protection data requirements for Conventional 158 (Indoor Use) and the April 2011 draft of 158W (All Other Uses)

The layout of the table below reflects the most current version of the 158W data requirements for determining toxicity to non-target plants from "All Other Uses" of antimicrobial pesticides, which would include indoor uses. In the rule proposed in 2008, this category was referred to as "Low Exposure" (see 73 FR 59382; October 8, 2008). In the April 2011 draft, these requirements are separated into tiers; however, this is not apparent from the accompanying data tables. Studies consisting of a single dose are termed "Tier One" while studies that use multiple doses (for characterizing dose/response relationship) are termed "Tier Two" (see 73 FR 59382, at 59416). In this "tiered" system, the algal plant growth test is required and higher tier tests are performed based on the results; however, there are triggers for additional testing based on physicochemical properties and exposure potential as well. These requirements have never been applied to conventional uses other than terrestrial and aquatic nonfood uses and forestry uses. Indoor uses have never required this category of testing.

Non-Target Plant Protection Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[5]**	**April 2011 158W Draft All Other Uses[6]**	**Range of Study Costs[7]**

[5] As listed in 40 CFR 158.

[6] Use patterns for Non-Target Plant Protection are the same as for the Non-Target Organisms Data Requirements.

Non-Target Plant Protection Data Requirements			
Test Guideline	**Conventional 158 Indoor Uses[5]**	**April 2011 158W Draft All Other Uses[6]**	**Range of Study Costs[7]**
Seedling emergence, Tier II (850.4225)	**NOT IN TABLE**	**CR** (required if "risk quotient from any aquatic plant growth Tier II study exceeds a level of concern")	Low: $ 20,375 High: $ 39,000
Vegetative vigor, Tier II (850.4250)	**NOT IN TABLE**	**CR** (not required where there are no potential exposures to plants, where the hydrolytic half-life is less than 5 days, or if there is biodegradation in 28 days)	Low: $ 24,500 High: $ 65,000
Aquatic plant growth (vascular), Tier II (850.4400)	**NOT IN TABLE**	**CR** (required if algal plant growth Tier II test demonstrates detrimental effects at less than 1 ppm; required if EP component expected to enhance TGAI toxicity)	Low: $ 35,155 High: $ 65,000
Aquatic plant growth (algal), Tier II (850.5400)	**NOT IN TABLE**	**R** (required for one algal species, *Selenastrum capricornutum*)	Low: $ 35,155 High: $ 78,000

[7] Except where otherwise noted, the range of costs for individual studies is defined at the lower end by EPA estimates and at the higher end by estimates provided to EPA by the ACC Biocides Panel as part of its comments on the draft 158 rule of October 8, 2008. See Docket EPA-HQ-OPP-2008-0110, comments dated April 6, 2009. Specifically, higher end estimates of study costs were derived by NERA Economic Consulting presented in Appendix A of these comments.

Non-Target Plant Protection Data Requirements			
Test Guideline	**Conventional 158** **Indoor Uses**[5]	**April 2011 158W Draft** **All Other Uses**[6]	**Range of Study Costs**[7]
Terrestrial field (850.4300)	**NR**	**CR** (New methods must be confirmed by independent laboratory; protocols must be approved by EPA; required on "case-by-case basis, based on the results lower tier plant protection studies, adverse incident reports, intended use pattern, and environmental fate characteristics indicating potential exposure")	Low: $ 111,863 High: $ 1,300,000
Aquatic field (850.4450)	**NR**	**CR** (New methods must be confirmed by independent laboratory; protocols must be approved by EPA; required on "case-by-case basis, based on the results lower tier plant protection studies, adverse incident reports, intended use pattern, and environmental fate characteristics indicating potential exposure")	Low: $ 260,000 High: $ 267,250 (note that NERA cost is the low value and EPA cost in high value)

Comparison of the Environmental Fate data requirements for Conventional 158 (Indoor Use) and the April 2011 draft of 158W (All Other Uses)

The layout of the table below reflects the most recent version of the 158W data requirements for determining fate and transport in the environment from "All Other Uses" of antimicrobial pesticides, which would include indoor uses. In the rule proposed in 2008, this category was referred to as "Low Exposure" (see 73 FR 59382; October 8, 2008). In the current draft (April 2011), these requirements are separated into tiers; however, this is not entirely apparent from the data tables. The initial "Tier One" tests in this case are the hydrolysis, photodegradation, and activated sludge, respiration inhibition (ASRI) studies. The results of these studies, along with additional physicochemical properties, determine the extent of the data required under the Toxicity and Fate in Wastewater Systems (an entirely new category of requirements). A weight-of-evidence analysis on all the aforementioned studies will determine the necessity for Mobility and Metabolism Studies (both of which are entirely new categories of requirements). Finally, the Dissipation (aquatic sediment) and Monitoring of US Waters study requirements are also new requirements which appear to be triggered on EPA best professional judgment as well as the results of lower tiered data (i.e. via a weight-of-evidence determination). Note that many of the laboratory studies require testing with a radiolabeled test material, which increases overall study cost.

Environmental Fate Data Requirements			
Test Guideline	**Conventional 158 Food Indoor Uses[8]**	**April 2011 158W Draft All Other Uses[9]**	**Range of Study Costs[10]**
Degradation Studies – Laboratory			

[8] As listed in 40 CFR 158.

[9] Use patterns are similar to those used for Non-Target Organisms and Plant Protection Data Requirements.

[10] Except where otherwise noted, the range of costs for individual studies is defined at the lower end by EPA estimates and at the higher end by estimates provided to EPA by the ACC Biocides Panel as part of its comments on the draft 158 rule of October 8, 2008. See Docket EPA-HQ-OPP-2008-0110, comments dated April 6, 2009. Specifically, higher end estimates of study costs were derived by NERA Economic Consulting presented in Appendix A of these comments.

Environmental Fate Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Uses**[8]	**April 2011 158W Draft** **All Other Uses**[9]	**Range of Study Costs**[10]
Hydrolysis (835.2120)	**CR** ("required for indoor uses where environmental exposure is expected to occur. Such sites include, but are not limited to, agricultural premises, in and around farm buildings and beehives")	**R**	Low: $ 25,230 High: $ 195,000
Photodegradation in water (835.2240)	**NR**	**R** (not required based on results of hydrolysis data or electronic absorption spectroscopy)	Low: $ 47,875 High: $ 195,000
Toxicity and Fate in Wastewater Systems			
Activated sludge, respiration inhibition [ASRI] (850.6800, OECD 209)	**NOT IN TABLE**	**R**	Low: $ 5,126 High: $7,800
Activated sludge, sorption isotherm (835.1110)	**NOT IN TABLE**	**CR** (required based on selected chemical characteristics; required if a metal, log K_{ow} equal to or greater than 3, or positively charged or polycationic, or dependent on results of ASRI and Ready biodegradability tests)	Low: $ 10,051 High: $ 26,000

Environmental Fate Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Uses[8]**	**April 2011 158W Draft** **All Other Uses[9]**	**Range of Study Costs[10]**
Ready biodegradability (835.3110)	**NOT IN TABLE**	**CR** (required based on results of ASRI and Ready biodegradability tests; not required if metal, relatively volatile but not hydrophobic, or highly reactive)	Low: $ 10,364 High: $ 13,000 (radiolabeling increases high end cost to $ 41,475)
Porous pot study (835.3220)	**NOT IN TABLE**	**CR** (required based on results ASRI test; not required if metal, relatively volatile but not hydrophobic, or highly reactive)	Low: $ 39,000 High: $ 41,413 (note that NERA cost is the low value and EPA cost in high value)
Simulation test to assess biodegradability discharged in wastewater (835.3280)	**NOT IN TABLE**	**CR** (required based on results of ASRI test; not required if metal, relatively volatile but not hydrophobic, or highly reactive)	**No study cost estimates were identified.**
Mobility Studies			
Leaching and absorption/desorption (835.1230, 835.1240)	**NR**	**CR** ("required based on WOE evaluation of results of hydrolysis, photodegradation in water, activated sludge sorption isotherm, biodegradability and ASRI tests")	Low: $ 27,757 High: $ 49,400 (note cost of is for both tests combined)
Metabolism Studies - Laboratory			

Environmental Fate Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Uses**[8]	**April 2011 158W Draft** **All Other Uses**[9]	**Range of Study Costs**[10]
Aerobic soil metabolism (835.4100)	**NR**	**CR** ("required based on WOE evaluation of results of hydrolysis, photodegradation in water, activated sludge sorption isotherm, biodegradability and ASRI tests")	Low: $ 94,375 High: $ 156,000
Anaerobic soil metabolism (835.4200)	**NR**	**CR** ("required based on WOE evaluation of results of hydrolysis, photodegradation in water, activated sludge sorption isotherm, biodegradability and ASRI tests")	Low: $ 71,250 High: $ 195,000
Aerobic aquatic metabolism (835.4300)	**NR**	**CR** ("required based on WOE evaluation of results of hydrolysis, photodegradation in water, activated sludge sorption isotherm, biodegradability and ASRI tests")	Low: $ 44,475 High: $ 182,000
Anaerobic aquatic metabolism (835.4400)	**NR**	**CR** ("required based on WOE evaluation of results of hydrolysis, photodegradation in water, activated sludge sorption isotherm, biodegradability and ASRI tests")	Low: $ 80,900 High: $ 182,000
Dissipation Studies - Field			

Environmental Fate Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Uses**[8]	**April 2011 158W Draft** **All Other Uses**[9]	**Range of Study Costs**[10]
Aquatic sediment (835.6200)	**NR**	**CR** (New methods must be confirmed by independent laboratory; protocol must be approved by EPA; required "based on potential for aquatic exposure and if WOE indicates active ingredient or principal transformation products are likely to have potential for persistence, mobility, nontarget aquatic toxicity, or bioaccumulation")	Low: $ 260,000 High: $ 267,250 (note that NERA cost is the low value and EPA cost in high value)
Ground and Surface Water Monitoring			
Monitoring of representative US waters (none)	**NOT IN TABLE**	**CR** (New methods must be confirmed by independent laboratory; protocol must be approved by EPA; required "if WOE indicates active ingredient or principal transformation products are likely to occur in nontarget freshwater, estuarine or marine waters such that human or environmental exposures are likely to occur")	Low: $ 215,833 High: $ 1,300,000 (note there is no draft Test Guideline upon which to reliably estimate cost)

Comparison of the Residue Chemistry data requirements for Conventional 158 (Indoor Use) and the April 2011 draft of 158W (All Other Uses)

The layout of the table below reflects the most current version of the 158W Residue Chemistry data requirements from "All Other Uses" of antimicrobial pesticides, which would include indoor uses. In the rule proposed in 2008, this category was referred to as "Low Exposure" (see 73 FR 59382; October 8, 2008). In the April 2011 draft, these requirements are separated into tiers; however this is not entirely apparent from the data tables. The tiering indicated in the data tables are discussed in the preamble to the April 2011 draft; however, there is only distinction between "higher tiered" studies and everything else according to the data tables. The "lower tier" Supporting Information is now required for indoor uses of antimicrobials, while the "higher tier" requirements are based on use pattern, not on the results of the lower tier data. The nature of residues on surface study along with the migration study are new data requirements, as are the conditional requirements for potable water, fish and irrigated crops. Finally, the conditions under which residue studies in plants and/or livestock, food handling and food processing establishments will be required (along with additional studies on milk, meat, eggs, etc.) have expanded well beyond the conventional requirements for indoor food uses. This expansion is due to the fact that, per the April 2011 draft, surfaces not previously considered food-contact would be regulated as food-contact surfaces. It should be noted that the costs of supporting studies necessary to obtain a new tolerance (i.e., dietary studies, analytical method validation studies, etc.) are not included here and incur significant cost increases – costs which are again exacerbated by the use of radiolabeled test material and necessary for many of these studies.

Residue Chemistry Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Food Uses**[11]	**April 2011 158W Draft** **All Other Uses**[12]	**Range of Study Costs**[13]
Supporting Information			

[11] As listed in 40 CFR 158.

[12] Use patterns for residue chemistry requirements are Agricultural Premise, Indirect Food, Direct Food and Aquatic.

[13] Except where otherwise noted, the range of costs for individual studies is defined at the lower end by EPA estimates and at the higher end by estimates provided to EPA by the ACC Biocides Panel as part of its comments on the draft 158 rule of October 8, 2008. See Docket EPA-HQ-OPP-2008-0110, comments dated April 6, 2009. Specifically, higher end estimates of study costs were derived by NERA Economic Consulting presented in Appendix A of these comments.

Residue Chemistry Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Food Uses**[11]	**April 2011 158W Draft** **All Other Uses**[12]	**Range of Study Costs**[13]
Proposed tolerance/exemption (860.1550)	**CR** (required if indoor use could result in residues in or on food or feed)	**R**	**No study cost estimates were identified.**[14] Estimated cost: $ 50,000 for all three Supporting Information requirements
Reasonable grounds in support of petition (860.1560)	**CR** (required if indoor use could result in residues in or on food or feed)	**R**	**No study cost estimates were identified.**[15] Estimated cost: $ 50,000 for all three Supporting Information requirements
Submittal of analytical reference standards (860.1650)	**CR** (required if indoor use could result in residues in or on food or feed)	**R**	**No study cost estimates were identified.**[16] Estimated cost: $ 50,000 for all three Supporting Information requirements
Food-contact surfaces or impregnated materials			

[14] The total cost to comply with the requirements of 860.1550, 860.1560, and 860.1650 (preparing a tolerance petition, etc.) is estimated at $50,000. The cost of supporting studies necessary to develop a new tolerance (i.e. dietary studies) are not included here.

[15] The total cost to comply with the requirements of 860.1550, 860.1560, and 860.1650 (preparing a tolerance petition, etc.) is estimated at $50,000.

[16] The total cost to comply with the requirements of 860.1550, 860.1560, and 860.1650 (preparing a tolerance petition, etc.) is estimated at $50,000. The cost of developing entirely new analytical standards to support a new tolerance are not included here.

Residue Chemistry Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Food Uses**[11]	**April 2011 158W Draft** **All Other Uses**[12]	**Range of Study Costs**[13]
Nature of residue on surfaces (none)	**NOT IN TABLE**	**CR** (required if "applied to a food contact surface or impregnated into a food-contact material and if theoretical (high end) estimates of exposure exceed EPA's risk level of concern"; protocols must be approved by EPA)	**No study cost estimates were identified.** (note there is no draft Test Guideline upon which to reliably estimate costs)
Migration studies (none)	**NOT IN TABLE**	**CR** (required "based on results of residue on surfaces study if residues of concern are identified"; protocols must be approved by EPA)	Low: $ 104,000 High: $ 105,000 (note there is no draft Test Guideline upon which to reliably estimate cost)
Higher Tiered			

Residue Chemistry Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Food Uses**[11]	**April 2011 158W Draft** **All Other Uses**[12]	**Range of Study Costs**[13]
Nature of residue in plants (860.1300)	**CR** (required for indoor use when applied directly to food; not required for indirect contact (e.g., crack and crevice treatment); may not be required for tolerance exemption based on low toxicity or theoretical estimates are adequate to assess dietary risk)	**CR** (required if crop plants or metabolically active RACs may be directly or indirectly exposed)	Low: $ 100,000 X 3 = $ 300,000 High: $ 390,000 X 3 = $ 1,170,000 (cost based on 1 species; however, test normally required in 3 crops and requires radiolabeled test material)
Nature of residue in livestock (860.1300)	**CR** (required if indoor use could result in residues in or on food or feed; required when pesticide is applied directly to livestock; may not be required for tolerance exemption based on low toxicity or theoretical estimates are adequate to assess dietary risk)	**CR** (required if livestock "may be exposed via the oral, dermal, or inhalation route following treatment or contamination of sites including but not limited to livestock premises, feed and drinking water")	Low: $ 105,833 X 2 = $ 211,666 High: $ 325,000 X 2 = $ 650,000 (cost based on 1 species; however, test normally required in 2 species and requires radiolabeled test material)
Potable water (860.1400)	**NR**	**CR** (required if applied directly to water or if water could be contaminated by run-off, leachate, or discharge from treated sites or materials and into potable water)	Low: $ 53,750 High: $ 130,000

Residue Chemistry Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Food Uses**[11]	**April 2011 158W Draft** **All Other Uses**[12]	**Range of Study Costs**[13]
Fish (860.1400)	**NR**	**CR** (required if applied directly to water of if water could be contaminated by run-off, leachate, or discharge from treated sites or materials and into water containing fish that may be used for human consumption)	Low: $ 104,000 High: $ 130,000
Irrigated crops (860.1400)	**NR**	**CR** (required if applied directly to water or if water could be contaminated by run-off, leachate, or discharge from treated sites or materials and into water used for irrigation of food crops)	Low: $ 18,000 High: $ 650,000 (NERA cost based on five crops)
Food handling (860.1460)	**CR** (required if residues could result in food or feed, if pesticides used in food or feed handling establishment)	**CR** (required when theoretical high-end estimates, radiolabeled data, or the nature of residue on surface studies demonstrate that residues could occur in food/feed)	Low: $ 195,000 High: $ 205,000 (note that NERA cost is the low value and EPA cost in high value)

Residue Chemistry Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Food Uses**[11]	**April 2011 158W Draft** **All Other Uses**[12]	**Range of Study Costs**[13]
Meat/milk/poultry/eggs (860.1480)	**CR** (required if indoor use could result in residues in or on food or feed ; required when pesticide is applied directly to livestock; not required if livestock residue studies indicate negligible transfer to tissue/milk/eggs; may not be required for tolerance exemption based on low toxicity or theoretical estimates are adequate to assess dietary risk)	**CR** (required if livestock "may be exposed via the oral, dermal, or inhalation route following treatment or contamination of sites including but not limited to livestock premises, feed and drinking water")	Low: $ 149,000 + $ 149,000 = $ 398,000 High: $ 260,000 + $ 195,000 = $ 455,000 (test required in meat/milk and poultry/eggs)
Crop field trials (860.1500)	**CR** [required for postharvest treatment of RACs (e.g. fungicidal waxes or stored grain fumigants); may not be required for tolerance exemption based on low toxicity or theoretical estimates are adequate to assess dietary risk]	**CR** (required "if food crops or metabolically active RACs may be exposed" ... including but not limited to "postharvest food and vegetable rinses, application to field crops, mushroom houses, empty or occupied beehives and wood used to construct beehives")	Low: $ 163,667 High: $ 975,000 (NERA estimate based on five crops)

Residue Chemistry Data Requirements			
Test Guideline	**Conventional 158 Food** **Indoor Food Uses**[11]	**April 2011 158W Draft** **All Other Uses**[12]	**Range of Study Costs**[13]
Processed food or feed (860.1520)	**CR** ("required if residues could potentially concentrate on processing thus requiring the establishment of a separate tolerance higher than that of the raw agricultural commodity")	**CR** (required if concentration upon processing is expected; could require a separate tolerance)	Low: $ 35,000 High: $ 650,000 (NERA estimate based on five commodities)

Comparison of the Toxicity data requirements for Conventional 158 (Direct Food Use) and the April 2011 draft of 158W (Indirect Food Use ≤ 200 parts per billion)

The layout of the table below reflects the most current version of the 158W data requirements for determining toxicity from indirect food use of an antimicrobial pesticide. This comparison is challenging as conventional 158 only refers to "food" and "nonfood" uses while the April 2011 draft rule refers to both "direct" and "indirect" food use patterns. In the case of indirect food uses, these are split into exposures less than/equal to and greater than 200 parts per billion. The confusion in this section has been imposed by removal of all references to "high human exposure" and "low human exposure" yet still relying on the functional categories to "tier" the data requirements per use patterns.[17] So while the data requirements for a "high exposure" Indirect Food Contact use (defined here as concentrations greater than 200 ppb) are no different than those for a Direct Food Contact use, both of these (duplicative) categories remain in the April 2011 draft. To add to this confusion, not only is there no definition in the regulation denoting what constitutes a "Direct Food Use" but use of this term runs contrary to its long-time use by FDA to denote either direct or indirect food additive uses.

[17] In the 2008 FR draft, the column now labeled Direct Food Uses was labeled High Human Exposure Uses. Examples of these uses were provided in the introductory section to the Toxicology Data Requirements table. When EPA deleted all mention of High Human Exposure Uses in the revised proposal, it deleted any explanation of the uses subject to the designation Direct Food Uses. In order to determine whether any of these uses include "direct food uses", it was necessary to review the preamble to the proposed 158W requirements at 73 FR 59382, 59401 (October 8, 2008).

Similarly, there are obstacles to determining the indirect food use categories mandated the proposed regulation. In the regulatory introduction to the Toxicology Data Requirements table, EPA states

> *"The 200 ppb was originally used by [FDA] with respect to the concentration of residues in or on food for tiering of data requirements for indirect foo use biocides. The Agency has also adopted this same residue level for determining toxicology data requirements for indirect food uses of antimicrobial pesticides. The 200 ppb is the concentration of antimicrobial residues in or on the food item."*

This provision is problematic for two reasons: (1) the FDA indirect food uses also include those that EPA now calls direct food uses; and (2) FDA's use of 200 ppb was a dietary food intake level and not a residue level in or on food items. These categories must be clarified in order to determine appropriate data requirements.

Toxicology Data Requirements				
Test Guideline	**Conventional 158 Food Use**	**April 2011 158W Draft Indirect Food Use (≤ 200 ppb)**	**April 2011 158W Draft Indirect Food Use (> 200 ppb) *or* Direct Food Use**	**Range of Study Costs[18]**
Acute neurotox (870.6200)	**R** (study route of exposure must correspond to primary route of exposure upon use)	**CR** (dependent on results of neurotox screening in 90-day oral "or other data indicate neurotoxicity")	**R**	Low: $ 89,596 High: $ 260,000
21/28-day dermal (870.3200)	**R** (required if use results in human exposure via skin contact and 90-day study not triggered)	**CR** (required if use results in repeated dermal human exposure and 90-day study not available/triggered; required if any EUP component may increase dermal absorption or enhance toxicity)	**CR** (required if use results in repeated dermal human exposure and 90-day study not available/triggered; required if any EUP component may increase dermal absorption or enhance toxicity)	Low: $ 83,240 High: $ 104,000

[18] Except where otherwise noted, the range of costs for individual studies is defined at the lower end by EPA estimates and at the higher end by estimates provided to EPA by the ACC Biocides Panel as part of its comments on the draft 158 rule of October 8, 2008. See Docket EPA-HQ-OPP-2008-0110, comments dated April 6, 2009. Specifically, higher end estimates of study costs were derived by NERA Economic Consulting presented in Appendix A of these comments.

Toxicology Data Requirements				
Test Guideline	**Conventional 158 Food Use**	**April 2011 158W Draft Indirect Food Use (≤ 200 ppb)**	**April 2011 158W Draft Indirect Food Use (> 200 ppb) *or* Direct Food Use**	**Range of Study Costs[18]**
90-day oral, non-rodent (870.3150)	**R** (1-year non-rodent study required if highly bioaccumulating or eliminated so slowly that steady state cannot be achieved in 90 days)	**CR** (required if "highly bioaccumulative or slowly eliminated"; results may trigger additional pharmacokinetic studies and/or longer duration non-rodent study)	**R**	Low: $ 221,047 High: $ 325,000
90-day dermal (870.3250)	**CR** (required if purposeful or prolonged dermal exposure from use, 90-day oral data not required, and/or dermal metabolism differs from oral)	**CR** (required if EPA determines primary route of exposure is dermal; required if any EUP component may increase dermal absorption or enhance toxicity; required if dermal metabolism differs from oral; required for HVAC use)	**CR** (required if EPA determines primary route of exposure is dermal; required if any EUP component may increase dermal absorption or enhance toxicity; required if dermal metabolism differs from oral; required for HVAC use)	Low: $ 137,094 High: $ 325,000
90-day inhalation (870.3465)	**CR** (required if repeat inhalation exposure at levels of concern are possible)	**CR** (required if EPA determines primary route of exposure is inhalation; required if there is "likelihood of significant repeated inhalation exposure to pesticide as gas, vapor, aerosol"; required for HVAC use)	**CR** (required if EPA determines primary route of exposure is inhalation; required if there is "likelihood of significant repeated inhalation exposure to pesticide as gas, vapor, aerosol"; required for HVAC use)	Low: $ 300,000 High: $ 394,000

Toxicology Data Requirements				
Test Guideline	**Conventional 158 Food Use**	**April 2011 158W Draft Indirect Food Use (≤ 200 ppb)**	**April 2011 158W Draft Indirect Food Use (> 200 ppb) *or* Direct Food Use**	**Range of Study Costs[18]**
90-day neurotox (870.6200)	**R** (study route of exposure must correspond to primary route of exposure upon use)	**CR** (dependent on results of neurotox screening in 90-day oral "or other data indicate neurotoxicity")	**R**	Low: $ 89,596 High: $ 260,000
Chronic oral, rodent (870.4100)	**R** (required if tolerance needed or if use is "likely to result in repeated human exposure over a considerable portion of the human lifespan")	**CR** (required if tolerance needed or if use is "likely to result in repeated human exposure over a considerable portion of the human lifespan"; may be required based on the results of acute, subchronic tests or "on other data indicating neurotoxicity")	**R**	Low: $ 650,000 High: $ 950,000 (note that NERA cost is the low value and EPA cost in high value)
Companion animal safety (870.7200)	**CR** (Domestic Animal Safety Data "required on a case by case basis")	**CR** (required if "product use will result in exposure to domestic animals, such as cats, dogs, cattle, pigs and horses")	**CR** (required if "product use will result in exposure to domestic animals, such as cats, dogs, cattle, pigs and horses")	Low: $ 156,000 High: $ 650,000

Toxicology Data Requirements				
Test Guideline	**Conventional 158 Food Use**	**April 2011 158W Draft Indirect Food Use (≤ 200 ppb)**	**April 2011 158W Draft Indirect Food Use (> 200 ppb) *or* Direct Food Use**	**Range of Study Costs[18]**
Dermal penetration (870.7600)	**CR** ("required for compounds having serious toxic effect as identified by oral or inhalation studies, for which a significant route of human exposure is dermal and for which assumption of 100 percent absorption does not produce an adequate margin of safety")	**CR** ("in absence of dermal absorption data or repeat dose dermal study, assumption of 100% absorption will be used in a risk assessment to determine if dermal penetration study is required")	**CR** ("in absence of dermal absorption data or repeat dose dermal study, assumption of 100% absorption will be used in a risk assessment to determine if dermal penetration study is required")	Low: $ 117,000 High: $ 147,529 (note that NERA estimate is the low end cost and EPA is the high end cost)