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MEMORANDUM

Via E-Mail

DATE: October 17, 2008

TO: Firm Clients and Friends

FROM: Bergeson & Campbell, P.C.

RE: EPA Publishes Proposed Antimicrobial Pesticide Data Requirements

On October 8, 2008, the U.S. Environmental Protection Agency (EPA) proposed to revise the data requirements applicable to antimicrobial pesticide products.¹ Comments on the proposed rule are due by **January 6, 2009**. EPA also has announced that it will host a public workshop about the proposed rule on **November 6, 2008**.² In addition to the proposed data requirements, EPA has requested comments on: (1) a white paper on structure-activity relationship information and modeling; (2) its proposed approach and related case studies for assessing the effects of antimicrobials on wastewater treatment plants; (3) data requirements for applications pending at the effective date for the final version of the proposed rule; (4) the 12 proposed use patterns; and (5) whether the data requirements should differ for wood preservatives that are for land-use only and those that are for both land and aquatic uses. Documents related to the proposed rule on which EPA requests comment are available in the e-docket, EPA-HQ-OPP-2008-0110, which is accessible at www.regulations.gov.

Background and Scope

The data requirements that currently apply to antimicrobial pesticide products are codified in 40 C.F.R. Part 161. First promulgated in their current form in 1984, these data requirements were developed primarily for agricultural pesticides and do not address antimicrobial use patterns specifically. EPA proposed data requirements for antimicrobial pesticides in 1999,³ which were subject to substantial comment and never issued in final. EPA

¹ 73 Fed. Reg. 59382 (Oct. 8, 2008).

² 73 Fed. Reg. 60211 (Oct. 10, 2008).

³ 64 Fed. Reg. 50672 (Sept. 17, 1999).



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revised the data requirements in 40 C.F.R. Part 158 applicable to conventional and biological pesticides in October 2007; at that time, the existing data requirements, with continuing applicability only to antimicrobials, were moved to Part 161. The proposed rule discussed in this memorandum would eliminate the current Part 161 and promulgate the revised requirements for antimicrobials in Part 158, subpart W.

By proposing newly codified data requirements, EPA states that it is seeking to add new data requirements to reflect changes in each of the applicable science disciplines, as well as incorporate data requirements that are not currently codified in the regulations but that EPA states it regularly requires as part of “current practices”⁴ under 40 C.F.R. Section 158.75.⁵ Additionally, EPA proposes to specify 12 use patterns for antimicrobial pesticides and indicate in data tables in subpart W which data requirements apply on a use-pattern basis. For several of the science disciplines, including toxicity, ecotoxicity, and environmental fate testing, EPA is proposing a tiered approach to data development. For those use patterns that are associated with lower exposures to humans and the environment, EPA proposes to require fewer studies initially; additional testing may be required subsequently based on the test results.

EPA clarifies that the data requirements in the proposed rule will apply not only to antimicrobial pesticides as defined in Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 2(mm), but also to: (1) pesticide products for antimicrobial uses on food or feed; (2) antifoulant paints and coatings; (3) wood preservatives; and (4) antimicrobial manufacturing-use products.⁶ EPA also states that the proposed regulatory revisions will set the data requirements not only for new registrations and registration amendments, but also for experimental use permits, registration review, and tolerance and tolerance exemption petitions. EPA states that the proposed data requirements, once final, will apply both to new and pending applications and encourages registrants with applications submitted before, but not approved by the time the new requirements go into effect, to confer with EPA about the data required for the specific application.⁷

⁴ 73 Fed. Reg. at 59387.

⁵ *Id.* at 59383.

⁶ *Id.* at 59385-59386.

⁷ *Id.* at 59388.



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Use Pattern and Index

EPA has proposed to organize antimicrobial products into 12 use patterns and specify data requirements applicable to each use pattern. The use patterns, which EPA describes as the same as those “employed in recent years,”⁸ are the following:

- Agricultural premises;
- Food-handling/storage establishments, premises, and equipment;
- Commercial, institutional and industrial premises and equipment;
- Residential and public access premises;
- Medical premises and equipment;
- Human drinking water systems;
- Materials preservatives;
- Industrial processes and water systems;
- Antifoulant paints and coatings;
- Wood preservatives;
- Swimming pools; and
- Aquatic areas.

In the preamble to the proposed rule, EPA requests comment on the proposed use patterns, and in particular whether they should be split, recombined, and/or have new patterns added. EPA also states its intent to place on its website an Antimicrobial Use Site Index, similar to the one at <http://www.epa.gov/pesticides/regulating/usesite/index.htm> for conventional and biological pesticides.

⁸ *Id.* at 59389.



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Product Chemistry

EPA proposes to apply the same product chemistry data requirements currently applicable to other pesticides to antimicrobial pesticides. These requirements are published in 40 C.F.R. Part 158, subpart D.

Product Performance

EPA states that the product performance data requirements in the proposed rule are “nearly identical” to those currently required. In addition, EPA is re-proposing definitions for the following terms, which EPA states are identical to the definitions contained in the September 17, 1999, proposed rule: disinfectant; fungicide; microbiological water purifier; sanitizer; sterilant, tuberculocide, and virucide.⁹ Finally, EPA also explicitly defines “public health claim” in the proposed rule.¹⁰

⁹ *Id.* at 59391.

¹⁰ *Public health claim.* An antimicrobial pesticide is considered to make a public health claim if the pesticide product bears a claim to control pest microorganisms that pose a threat to human health, and whose presence cannot readily be observed by the user, including but not limited to, microorganisms infectious to man in any area of the inanimate environment. A product makes a public health claim if one or more of the following apply:

(1) A claim is made for control of specific microorganisms or classes of microorganisms that are directly or indirectly infectious or pathogenic to man (or both man and animals). Examples of specific microorganisms include, but are not limited to, *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Escherichia coli* (*E. coli*), *human immunodeficiency virus* (*HIV*), *Streptococcus*, and *Staphylococcus aureus*. Claims for control of microorganisms infectious or pathogenic only to animals (such as canine distemper virus or hog cholera virus) are not considered public health claims.

(2) A claim is made for the pesticide product as a sterilant, disinfectant, virucide, sanitizer, or tuberculocide regardless of the site of use of the product, and regardless of whether specific microorganisms are identified.



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Mammalian Toxicity

As for conventional pesticides, the types of toxicology studies required for assessment of antimicrobials include acute, subchronic, and chronic studies, as well as carcinogenicity, prenatal developmental and reproductive toxicity, mutagenicity, neurotoxicity, immunotoxicity, and other studies. For antimicrobial pesticides, EPA proposes to divide proposed uses into high- and low-exposure groups; EPA proposes initially to require 13 toxicity studies for the low-exposure group, and 19 for the high-exposure group.¹¹ Additional studies may be required later for the low-exposure group, depending on the initial study results.

(3) A claim is made for the pesticide product as a fungicide against fungi infectious or pathogenic to man, or the product does not clearly state that it is intended for use only against non-public health fungi.

(4) A claim is made for the pesticide product as a microbiological water purifier or microbial purification system.

(5) A non-specific claim is made that the pesticide product will beneficially impact or affect public health at the site of use or in the environment in which applied (such as a 'sanitary' claim), and:

(i) The pesticide product contains one or more ingredients that, under the criteria in 40 CFR 153.125(a), is an active ingredient with respect to a public health microorganism and there is no other functional purpose for the ingredient in the product; or

(ii) The pesticide product is similar in composition to a registered pesticide product that makes explicit antimicrobial public health claims.

Id. at 59431 (to be codified at 40 C.F.R. § 158.2203(b)).

¹¹ EPA proposes to require the following studies for all antimicrobial products: acute oral, dermal, and inhalation toxicity; primary eye and dermal irritation; dermal sensitization; a rodent subchronic toxicity study; prenatal developmental toxicity studies in two species; a two-generation reproductive study; mutagenicity studies; and immunotoxicity testing. Additionally, for high-human exposure uses, EPA proposes to require the following additional studies: acute and subchronic neurotoxicity testing; a chronic feeding study in



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According to EPA's proposal, "high human exposure uses" include but are not limited to:

- (i) Any use which requires a tolerance or tolerance exemption (except for indirect food uses requiring a tolerance or tolerance exemption in which residues are less than 200 [parts per billion] ppb).
- (ii) Indirect food uses with residues equal to or greater than 200 ppb.
- (iii) Use in human or animal drinking water.
- (iv) Fruit and vegetable rinses.
- (v) Egg washes.
- (vi) Swimming pools.
- (vii) Outdoor aquatic uses in lakes, rivers or streams which have the potential to contaminate potable water.
- (viii) Wood preservatives.
- (ix) Metalworking fluids.¹²

EPA defines low human exposure uses to be those that are not high exposure uses.

Human Exposure Data

For antimicrobial pesticides, EPA proposes to require three types of human-exposure data: applicator, post-application, and residue chemistry (the third of which is discussed in the next section). EPA states that the proposed data requirements reflect EPA's current practice of requiring exposure data "when certain toxicity and exposure criteria are met,"¹³ as set forth in proposed Sections 158.2260 and 158.2270. In the preamble to the proposed rule, EPA reminds applicants that research undertaken to address these data requirements and that involves the intentional dosing of human subjects must first be reviewed by the Human Studies Review Board. EPA also states that surrogate data may be used whenever appropriate, and references the ongoing work of the Antimicrobial Exposure Assessment Task Force in particular.¹⁴

one species; carcinogenicity studies in two species; and a mammalian metabolism study. *Id.* at 59433 (to be codified in the data tables at 40 C.F.R. § 158.2230(d)).

¹² *Id.* at 59432 (to be codified at 40 C.F.R. § 158.2230(b)(1)).

¹³ *Id.* at 59398.

¹⁴ *Id.*



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Residue Chemistry

EPA has proposed residue chemistry data requirements for antimicrobial products that are similar to the requirements for conventional chemicals in that the same types of data will be required (*e.g.*, directions for use, proposed tolerance and reasonable grounds in support of the petition, data characterizing the nature and magnitude of the residue, and analytical methods), though the specific requirements have been adapted for antimicrobials. In the proposal, EPA creates the following four use-related categories and specifies the data requirements for each use category: direct and indirect food uses; agricultural premises; and aquatic uses.¹⁵

As examples of direct food uses, EPA lists: livestock and feed; drinking water; egg washes; fruit and vegetable rinses; aquatic areas that have the potential to contaminate potable water; and post-harvest applications. According to EPA, “[n]o currently registered antimicrobial products are applied to agricultural field crops,” but if such an application were to be submitted to EPA, EPA states that it likely would require the same data required for conventional field-use pesticides in addition to the ones specified in proposed subpart W.¹⁶

The proposed rule provides an illustrative description of indirect food uses:

[S]uch as antimicrobial products applied to a surface or incorporated into a material that may contact food or feed. Residues may be expected to transfer to such food or feed. Data are required regardless of whether the antimicrobial is applied or impregnated for the purpose of imparting antimicrobial protection to the external surfaces of the substance or article, or for the purpose of protecting the substance or article itself.¹⁷

EPA states that indirect food uses include products labeled for treatment of hard non-porous surfaces that may come into contact with food. EPA further states that, “[h]ard surfaces are considered to be food surfaces when food is prepared for consumption, either commercially or

¹⁵ *Id.* at 59401 (to be codified at 40 C.F.R. § 158.2290).

¹⁶ *Id.*

¹⁷ *Id.* at 59444 (to be codified at 40 C.F.R. § 158.2290(b)(1)(ii)).



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residentially on such surfaces,” and lists several examples including cutting boards, countertops, refrigerator shelves and bins.¹⁸

Environmental Risk Assessment

As with mammalian testing, EPA proposes to divide antimicrobials into high- and low-environmental exposure groups and specify environmental fate, toxicity, and plant protection data requirements based on the grouping. EPA states that it believes there is high environmental exposure potential for three of the proposed 12 antimicrobial use patterns, and part of a fourth: antifoulant paints and coatings; wood preservatives; aquatic areas; and once-through industrial processes and water systems (which is part of the industrial processes and water systems use pattern).¹⁹ The rest of the use patterns would be included in the low environmental exposure group. EPA states in its proposal that it plans to continue to distinguish the data requirements for wood preservatives that are for land-use only and those that are for both land and aquatic use but specifically requests comment on this aspect of its proposal.

Environmental Fate

In its proposal for environmental fate data, EPA particularly focuses on effects to sewer systems and wastewater treatment plants (WWTP). EPA states that historically, it assumed dilution, degradation, or removal by WWTP processes would mitigate environmental concerns. EPA further states that information about detection of antimicrobial chemicals in the environment and questions raised about the effect of antimicrobial products on WWTP processes have caused it to rethink its requirements.²⁰ Under its proposed tiered approach, EPA would require a limited number of studies for low environmental exposure use patterns, and use these data to support down-the-drain screening modeling. As stated above, EPA specifically is requesting comment on its screening model and related case studies, copies of which are included in the docket for this rulemaking. Additional studies could be required depending on the results of the modeling, as well as for products with high environmental exposure uses.²¹

¹⁸ *Id.* at 59402.

¹⁹ *Id.* at 59405.

²⁰ *Id.* at 59406-59407.

²¹ Data requirements for products with low environmental exposure use patterns would include: hydrolysis; photodegradation in water; activated sludge sorption isotherm; ready biodegradability; and modified activated sludge, respiration inhibition test. Additional



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Environmental Toxicity

EPA proposes to require the following three studies for all antimicrobials: avian acute oral toxicity; acute freshwater fish toxicity; and acute freshwater invertebrate toxicity. Depending on the specific use, high environmental exposure uses may trigger additional testing initially, such as additional avian or aquatic toxicity studies, sediment testing, and testing of a typical end-use product. EPA proposes a range of additional testing, conditional upon the results of the first tier studies as well as the proposed use.²²

Plant Protection

EPA proposes to require one study initially for products with low environmental exposure use patterns: aquatic plant growth (algal) Tier II study (dose response), a multiple-dose study. EPA proposes to require for high environmental exposure use patterns, and conditionally require for all products meeting the triggering criteria, several additional plant protection studies, all of which are Tier II dose response studies:²³ seedling emergence; vegetative vigor; aquatic plant growth (aquatic vascular plant); and terrestrial and aquatic field studies.²⁴

Alternate Testing Approaches

In the preamble to the proposed rule, EPA states that it “is committed to moving towards a more efficient and refined testing/risk assessment paradigm” that would “reduce the use of animal testing, take full advantage of advances in science, and provide a sufficient,

studies required for high environmental exposure use patterns or conditionally required for all use patterns include: porous pot study; leaching and adsorption/desorption; laboratory metabolism studies; and field dissipation studies. *Id.* at 59442-59443 (to be codified at 40 C.F.R. § 158.2280(e)).

²² *Id.* at 59436 (to be codified at 40 C.F.R. § 158.2240).

²³ EPA states that, “If the applicant is in possession of single-dose studies that the applicant believes provide sufficient information, then the applicant is encouraged to consult early in the application process with EPA.” Otherwise, the multiple-dose studies must be conducted. *Id.* at 59416.

²⁴ *Id.* at 59439 (to be codified at 40 C.F.R. § 158.2250).



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credible amount of data for use in a risk assessment.”²⁵ EPA further states: “It would be a poor use of societal resources to routinely require the submission and governmental review of a multi-million dollar database for every active ingredient if there were alternative methods of determining which chemicals could be evaluated in a scientifically rigorous manner using means other than measured data.”²⁶ To this end, as discussed above, EPA has placed and requested comments on a paper in the docket for this rulemaking titled, “Use of Structure-Activity Relationship (SAR) Information and Quantitative SAR (QSAR) Modeling For Fulfilling Data Requirements for Antimicrobial Pesticide Chemicals and Informing EPA’s Risk Management Process.” EPA also discusses its continuing efforts with the International Life Sciences Institute and Health and Environmental Sciences Institute project and with computational toxicology; and discusses the results of the National Academy of Sciences reports concerning toxicity testing and assessment of environmental agents.²⁷

Other Items of Interest

The preamble to the proposed rule discusses the status of EPA’s international efforts as they relate to antimicrobial products, including joint data reviews and evaluations, data requirement harmonization, and protocol/guideline harmonization. EPA also discusses recent (2006) revisions to the regulations that govern human testing, codified in 40 C.F.R. Part 26, and reiterates the potential applicability of these rules, and in particular the requirement of review by the Human Studies Review Board before a study is initiated, to some of the data requirements proposed in this rulemaking.²⁸

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We hope this information is helpful. As always, please call if you have any questions.

²⁵ *Id.* at 59421.

²⁶ *Id.*

²⁷ *Id.* at 59423-59424.

²⁸ *Id.* at 59419-59420.