ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 158 and 161

RIN 2070–AD30

Data Requirements for Antimicrobial Pesticides

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA proposes to revise and update the existing data requirements for antimicrobial pesticides. The proposed revisions are needed to reflect current scientific knowledge and current Agency regulatory practices, and to improve protection of the general population as well as sensitive subpopulations. The proposed requirements are intended to further enhance the Agency's ability to make regulatory decisions about the human health and environmental fate and effects of antimicrobial pesticide products.

DATES: Comments must be received on or before January 6, 2009.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2008–0110, by one of the following methods:

• *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

• *Mail*: Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001.

• *Delivery*: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA 22202. Deliveries are only accepted during the Docket's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305–5805.

Instructions: Direct your comments to docket ID number EPA–HQ–OPP–2008–0110. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at *http://www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The regulations.gov website is an ''anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the docket index available in regulations.gov. To access the electronic docket, go to *http://www.regulations.gov*, select ''Advanced Search,'' then ''Docket Search.'' Insert the docket ID number where indicated and select the ''Submit'' button. Follow the instructions on the regulations.gov website to view the docket index or access available documents. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov*, or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA 22202. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Kathryn Boyle, Field and External Affairs Division, Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; mail code 7506P; telephone number: 703–305–6304; fax number: 703–305–5884; e-mail address: *boyle.kathryn@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be affected by this action if you are a producer of pesticide products (NAICS 32532), antifoulants (NAICS 32551), antimicrobial pesticides (NAICS 32561) or wood preservatives (NAICS 32519), importers of such products, or any person or company who seeks to register an antimicrobial, antifoulant coating, ballast water treatment, or wood preservative pesticide or to obtain a tolerance for such a pesticide. This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed above could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, please contact Norm Cook, Chief of the Risk Assessment and Science Support Branch in the Antimicrobials Division of the Office of Pesticide Programs at 703–308–8253 or via email, cook.norm@epa.gov.

B. What Should I Consider as I Prepare My Comments for EPA?

1. *Docket*. EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2008–0110. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov*, or, if only available in hard copy, at the Office of Pesticide Programs (OPP) Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA 22202. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

2. *Tips for preparing your comments*. When submitting comments, remember to:

i. Identify the document by docket ID number and other identifying information (subject heading, **Federal Register** date and page number).

ii. Follow directions. The Agency may ask you to respond to specific questions or organize comments by referencing a Code of Federal Regulations (CFR) part or section number.

iii. Explain why you agree or disagree; suggest alternatives and substitute language for your requested changes.

iv. Describe any assumptions and provide any technical information and/or data that you used.

v. If you estimate potential costs or burdens, explain how you arrived at your estimate in sufficient detail to allow for it to be reproduced.

vi. Provide specific examples to illustrate your concerns and suggest alternatives.

vii. Explain your views as clearly as possible, avoiding the use of profanity or personal threats.

viii. Make sure to submit your comments by the comment period deadline identified.

II. Background

A. What Action is the Agency Taking?

The Environmental Protection Agency (EPA or the Agency) is proposing to establish a separate listing of the data requirements for antimicrobial pesticides in Title 40 of the Code of Federal Regulations (CFR) in subpart W of part 158. This proposal sets out use patterns that are designed to make it easier to determine which requirements apply to antimicrobial products. In addition to retaining most current data requirements for antimicrobials, this proposal incorporates nine new data requirements and revises other existing data requirements. This rule, once final, is intended to further enhance the Agency's ability to make regulatory decisions about the human health, and environmental fate and effects of antimicrobial pesticide products.

The Agency has previously issued updated data requirements for conventional pesticides, and biochemical and microbial pesticides in part 158. This proposal is part of a larger effort to update and improve all of the data requirements for pesticide regulatory purposes. Data requirements for antimicrobial pesticides, currently contained in part 161, are proposed to be revised and included in part 158 upon promulgation.

Generally, antimicrobials are considered to be those chemicals that disinfect and sanitize. However, within this proposal EPA is using the term antimicrobials to collectively refer to antimicrobial pesticides, antifoulant coatings and paints, and wood preservatives.

As discussed in Unit XVIII.A., EPA has prepared a white paper entitled ''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,'' a copy of which is contained in the docket for this proposed rule (Ref. 43). The white paper discusses the current level of information and usage of structure-activity-relationship (SAR) assessments and Quantitative SAR (QSAR) modeling to fulfill data requirements in the Pesticide Program. The Agency specifically seeks comment on this support document.

Since many antimicrobial pesticides are typically rinsed down the drain, EPA has considered the potential impacts of pesticides that are discharged into wastewater treatment plants (WWTPs). This proposed rule addresses the issue of down-the-drain antimicrobials by proposing four new data requirements for use in a screening-level assessment on the fate of antimicrobials that reach a WWTP. To assess the impacts of this screening assessment and utility of the new data requirements for decision-making, EPA prepared four case studies (Ref. 42). The case studies, copies of which are contained in the docket for this proposed rule, are discussed in more detail in Unit XII.D. The Agency specifically seeks comment on the proposed approach for evaluating the potential impact of antimicrobial pesticide chemicals on WWTPs and nontarget organisms in receiving water bodies, and on the case studies, including the assumptions used in those studies, that were used to develop the proposed approach. EPA will consider comments specific to the case studies along with comments on the proposed approach, as the Agency evaluates the use of the proposed approach for down-the-drain antimicrobials in the final rule for antimicrobial data requirements.

On October 26, 2007, EPA promulgated final rules establishing data requirements for conventional pesticides (72 FR 60934), and biochemical pesticides and microbial pesticides (72 FR 60988). These final rules were effective on December 24, 2007, and are therefore the current part 158. As part of those actions, on October 24, 2007, (72 FR 60251) EPA preserved the original part 158 data requirements to provide continued regulatory coverage for antimicrobial pesticides until the Agency could promulgate a final regulation. To accomplish this, EPA transferred intact the original 1984 data requirements of part 158 into a new part 161, entitled ''Data Requirements for Antimicrobial Pesticides.'' Part 161, which applies only to antimicrobial pesticides, contains the current data requirements for antimicrobial pesticide chemicals.

As explained in the preamble to the conventional pesticide final rule, EPA intended to preserve the existing data requirements for antimicrobial pesticides until a new rule tailored specifically to antimicrobial pesticides could be promulgated. Part 161 is intended to be transitional. Once subpart W of part 158 is promulgated, there will be no need for part 161. Accordingly, EPA proposes to revoke part 161 upon the effective date of a final rule arising from today's proposal.

B. Reasons for Today's Action

Since the promulgation of part 158 in 1984, the Agency has recognized that the tables and test notes promulgated in 1984 failed to adequately address the unique applications, use patterns, and other factors germane to antimicrobial pesticides. Part 158 specifies the types of data and information generally required for making sound regulatory judgments under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The types of actions for which these data are needed include experimental use, registration, amended registration, reregistration, or registration review (collectively referred to in this proposal as ''registration''). The information required under FIFRA for registration of food-use pesticides is also information the Agency needs in order to grant tolerances or exemptions from the requirement of tolerances under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA).

Required data are intended to provide information about the potential adverse effects of uses of pesticides, and to define what is generally expected from applicants for registration in support of their products. However, it must be emphasized that each applicant has the continuing obligation under FIFRA to demonstrate that an individual product meets the standard for registration under section 3 of FIFRA or section 408 of FFDCA. Accordingly, as indicated in current § 158.75 and § 161.75, additional data may be needed to reflect the characteristics and use of specific pesticide products under review.

Since the data requirements now set out in part 161 (formerly part 158) were first published in 1984, every disciplinary area and requirement has been reconsidered and many have been revised in practice. These changes have been needed because the state of the science underlying the data requirements has advanced, and because the Agency has learned in specific registration actions that additional or different data are necessary to make sound regulatory decisions. These case-by-case decisions have been made in accordance with § 158.75, which allows the Agency to impose additional data requirements

beyond those specified in part 158 and now part 161.

Use patterns specific to antimicrobial pesticides are not specified in part 161, as they were not set out separately when originally promulgated in 1984. As a result, applicants have needed to interpret the data requirements often via extensive consultation with and interpretation from the Agency to determine the antimicrobial data requirements for a particular product. Today, EPA is proposing that the antimicrobial pesticide requirements be codified in a separate subpart W to part 158 with use patterns (see Unit IV.I. of this preamble) and groups of use patterns specific to antimicrobials.

Today's proposed rule is part of a series of rules to update all of the data requirements for pesticide products. On October 26, 2007, EPA published in the **Federal Register** two final rules to promulgate the data requirements for conventional (72 FR 60934), and biochemical and microbial (72 FR 60988) pesticide chemicals. These rules and their proposals (conventional (March 11, 2005) (70 FR 12276) and biochemical and microbial (March 8, 2006) (71 FR12072)) state the rationales for requiring and/or revising particular data requirements. With few exceptions, these rationales are also applicable to antimicrobial pesticide chemicals, and as such have not been repeated in today's proposed rule. Today's proposal discusses in detail only those revisions that are singularly applicable to antimicrobial pesticides, including antifoulants and wood preservatives.

C. Benefits of this Proposal

Greater detail on the benefits of this proposal is provided in the document entitled ''Economic Analysis of the Proposed Change in Data Requirements for Antimicrobial Pesticides'' which is available in the docket for this rulemaking (Ref. 44). The following briefly highlights the anticipated benefits:

1. *More refined assessments mean less uncertainty and clearer understanding of actual risks*. EPA's current applicator/user exposure data base is not comprehensive, especially regarding exposures to antimicrobials in industrial and residential settings. The new data that would be collected once this proposal becomes final would allow the Agency to conduct improved pre- and post-application exposure assessments for applicators/users, and the general public. This will benefit not only workers (including applicators) and consumers by helping EPA to make better informed regulatory decisions that are neither too stringent nor too lenient, but also benefit the regulated industry by reducing the uncertainty in Agency risk assessments. Thus, today's proposal will reduce, but not eliminate, uncertainty related to the risks posed by antimicrobial pesticides.

2. *Clarity and transparency to regulated community means savings*. The enhanced clarity and transparency of the information presented in part 158, subpart W should enhance the ability of industry to efficiently manage their antimicrobial registration submissions. Applicants may save time and money by understanding when studies are needed. Having all required studies available to EPA at the time of application should halt potential delays in the registration process, thereby enabling registration of antimicrobial pesticides sooner. Products would enter the market faster.

3. *EPA information assists other communities in assessing pesticide risks*. Scientific, environmental, and health communities find antimicrobial pesticide toxicity information useful to respond to a variety of needs. For example, medical professionals are concerned about the health of patients exposed to antimicrobials; poison control centers use and distribute information on toxicity and treatment associated with poisoning; and scientists use toxicity information to characterize the effects of antimicrobial pesticides and to assess risks of pesticide exposure. Similarly, those responsible for protection of nontarget wildlife need reliable information about antimicrobial pesticides and assurance that pesticides do not pose an unreasonable threat. The proposed changes will help the scientific, environmental, and health communities by increasing the breadth, quality, and reliability of Agency regulatory decisions by improving their scientific underpinnings.

4. *Better informed users mean informed risk-reduction choices*. Better regulatory decisions resulting from the proposed changes should also mean that the label will provide better information on the use of the antimicrobial pesticide. A pesticide label is the user's direction for using pesticides safely and effectively. It contains important information about where to use (or not use) the product, health and safety information to be read and understood before using a pesticide product, and how to dispose of that product. This benefits users by enhancing their ability to obtain antimicrobial pesticide products appropriate to their needs, and to use and dispose of products in a manner that is safe and environmentally sound. Applicators/users may benefit from label information based on the data submitted to the extent it helps inform their decisions about whether or how to use particular pesticides to avoid potential exposure.

D. What is the Agency's Authority for Taking this Action?

This action is issued under the authority of sections 3, 4, 5, 10, 12, and 25 of FIFRA as amended and section 408 of FFDCA. The data required for a registration, reregistration, experimental use permit, or tolerance are listed in 40 CFR part 158.

III. Statutory and Historical Framework

A. FIFRA

Under FIFRA section 3, every pesticide product must be registered with EPA or specifically exempted under FIFRA section 25(b) before being sold or distributed in the United States. Under FIFRA, an applicant for a new registration or an existing registrant (collectively referred to as applicant in this proposal) must demonstrate to the Agency's satisfaction that, among other things, the pesticide product, when used in accordance with widespread and commonly recognized practice, will not cause ''unreasonable adverse effects'' to humans or the environment. This safety determination requires the Agency to weigh the risks of the use of the pesticide against any benefits. EPA must determine that the standard for registration contained in FIFRA is met before granting a registration.

1. *Registration*. Section 3 of FIFRA contains the requirements for registration. Specifically, FIFRA section 3(c)(2) provides EPA broad authority, before and after registration, to require scientific testing and submission of the resulting data to the Agency by applicants for registration of pesticide products. An applicant must furnish EPA with substantial amounts of data on the pesticide, its composition, toxicity, potential human exposure, environmental properties, and ecological effects, as well as information on its product performance (efficacy) in certain cases. Although the data requirements are imposed primarily as a part of initial registration, EPA is authorized under FIFRA section 3(c)(2)(B) to require a registrant to develop and submit additional data to maintain a registration.

2. *Reregistration*. FIFRA section 4 requires that EPA reregister each pesticide product first registered before November 1984. This date was chosen because pesticides registered after 1984 were subject to the part 158 requirements of the 1984 regulation.

EPA has completed the reregistration/tolerance reassessment process for food-use pesticides and expects to complete all reregistration activities by the statutory deadline of August 2008.

3. *Registration review*. FIFRA section 3(g) mandates that the registrations of all pesticides are to be periodically reviewed. Changes in science, public policy, and pesticide use practices occur over time. Through the new registration review program implemented via a regulation promulgated on August 9, 2006 (71 FR 45719) (40 CFR part 155, subpart C), the Agency is periodically reevaluating all registered pesticides to assure that they continue to meet the statutory standard of no unreasonable adverse effects. Starting in 2006, registration review began to replace EPA's reregistration program as the mechanism for systematic review of existing pesticides. The registration review process begins by reviewing the available information in the possession of the Agency and then determining the specific data needed for assessing a particular pesticide. Thus, the data needed, and the scope and depth of the Agency's review will be tailored to the specific circumstances of a particular pesticide. This means that reviews will be commensurate with the complexity of the issues associated with each pesticide.

4. *Experimental Use Permits (EUPs)*. Subject to some exceptions, FIFRA section 5 requires persons seeking permission for experimental use of a pesticide under controlled condition to obtain an experimental use permit. A EUP allows limited use of a pesticide for specified experimental and data collection purposes intended to support future registration of the pesticide. Because a EUP is for limited use under controlled conditions, the data needed to support issuance of the permit are correspondingly less than those required for full registration. The regulations governing the issuance of EUPs are found in 40 CFR part 172. In its final rule ''Data Requirements for Conventional Pesticides'' EPA promulgated subpart C of part 158 to contain the data requirements for EUPs, which will be applied on a case-by-case basis to any EUP applications for an antimicrobial pesticide.

5. *Registration requirements for antimicrobials*. FIFRA section 3(h) requires that EPA evaluate its registration process to identify improvements and reforms that will reduce historical review times for antimicrobial applications. This includes defining the classes of antimicrobial use patterns and the types of application review, conforming reviews to risks and benefits, ensuring efficacy, and meeting review time goals. EPA believes that this rule assists in meeting the section 3(h) mandate. By defining the 12 use patterns for antimicrobials in relation to the data required for a registration under FIFRA, EPA is providing clearer and more transparent information to applicants. This should result in submissions to EPA that contain the required data and therefore can be reviewed and evaluated more expeditiously.

B. FFDCA

FFDCA requires EPA to determine that the level of pesticide chemical residues in food and feed will be safe for human consumption. The safety standard set under FFDCA section 408(b) and (c) defines safe as ''a reasonable certainty that no harm'' will result from exposures to pesticide chemical residues. The combination of aggregate and cumulative exposure assessments required by FFDCA section 408 increases the nature and scope of EPA's risk assessment, and potentially increases the types and amounts of data needed to determine that the FFDCA safety standard is met.

Under FFDCA section 408, EPA is authorized to establish tolerances for pesticide residues in food and feed, or to exempt a pesticide from the requirement of a tolerance, if warranted. In this preamble, references to tolerances include exemptions from tolerance since the standards and procedures for both are the same. The safety standard applies to tolerances in a number of regulatory situations, including:

- Tolerances that support registration under FIFRA;
- Tolerances for imported products which are established to allow importation of pesticide-treated commodities, but for which no U.S. registration is sought;
- Time-limited tolerances which are established for FIFRA section 18 emergency exemptions; and
- Temporary tolerances established for experimental use permits under FIFRA section 5.

C. Linking FIFRA and FFDCA Safety Standards

Under FIFRA section 2(bb), a pesticide that is inconsistent with, or does not meet, the FFDCA section 408 safety standard poses an unreasonable adverse effect that precludes new or continued registration. Given this linkage between registration and tolerances, it makes sense for EPA to define data requirements for both purposes: The data required to support a determination of ''reasonable certainty of no harm'' under FFDCA are an integral part of the data needed for an ''unreasonable adverse effects'' determination under FIFRA. Consequently, when promulgated, these proposed data requirements would encompass the basic data requirements for both registration and tolerance-setting determinations. EPA has authority to require additional data on a case-by-case basis.

D. Scope of Proposed Subpart W

FIFRA contains a number of provisions specific to ''antimicrobial pesticides'' as defined in FIFRA section 2(mm). The statutory definition contains a complex construction of functionality, types of organisms, and intended use to describe what is encompassed by the term ''antimicrobial pesticide.'' EPA believes that the definition was primarily intended to be used in conjunction with the provisions of section 3(h), which contains requirements for process improvements, timeframes for review purposes, and other regulatory matters, but, significantly, does not include provisions pertaining to data requirements. The definition in section 2(mm) as it relates to section 3(h) was discussed fully in a proposed rule issued in the **Federal Register** of September 17, 1999 (64 FR 50672).

The statutory definition, however, does not mesh with the Agency's needs in developing this proposed rule concerning data requirements. Data requirements depend upon the use pattern, taking into account the pesticide's hazard and exposure profiles. How well the pesticide kills or repels particular pests are relevant factors in the determination of product performance data requirements.

Neither FIFRA section 3(c)(2) nor section 3(h) requires the Agency to develop data requirements for an ''antimicrobial pesticide'' as defined specifically in section 2(mm). Therefore, the scope of this proposal has been expanded beyond ''antimicrobial pesticide'' as defined by FIFRA section 2(mm) to include related pesticides that are excluded from the 2(mm) definition. The broader applicability of this 40 CFR part 158, subpart W is intended to ensure that all pesticides currently considered as antimicrobial products for purposes of FIFRA section 33 fees and review periods are covered.

Accordingly, this proposal applies to:

- Antimicrobial pesticides, as defined in FIFRA section 2(mm).
- Pesticide products for antimicrobial uses in/on food or feed.
- Antifoulant paints and coatings.

- Wood preservatives.
- Pesticide products intended to be manufactured into any of the above.

IV. Introduction to Subpart W

A. Data Requirements for Registration

First promulgated in 1984, EPA's pesticide data requirements outline the kinds of data and related information typically needed to register a pesticide. In this proposal, the data requirements are organized by scientific discipline (e.g., toxicology), just as the existing data requirements in part 158 for conventional, and biochemical and microbial pesticides and those in part 161 for antimicrobials. A significant change in this proposal from the existing data requirements in part 161 is the introduction of 12 use patterns specific to antimicrobials. Since there is much variety in pesticide chemistry, exposure, and hazard, the requirements are designed to be flexible. Test notes to the data requirements tables explain the conditions under which data are typically needed. Essentially, the data requirements identify the questions that the applicant will need to answer regarding a pesticide product before the Agency can register it. Data requirements address both components of a risk assessment, i.e., the hazards that the pesticide presents, and the estimated level of exposure to humans or nontarget species. Having the appropriate information enables the Agency to understand when those hazards pose risks. The answer to one question may inform the kind of information needed to answer other questions. For example, a pesticide that is persistent and toxicologically potent may require more extensive exposure data to help establish a safe level of exposure. In addition, because a number of antimicrobials are used for public health purposes (for example, disinfectants, sterilants, or sanitizers), there are product performance data requirements to assure that the antimicrobial product works as intended.

B. Structure of Part 158

At this time data requirements for conventional, biochemical, and microbial pesticides are established in 40 CFR part 158. Data requirements for antimicrobial pesticides are established in 40 CFR part 161.

Part 158 contains general provisions concerning all pesticide data (subpart A), instructions on how to use the data tables that follow (subpart B), and a series of disciplinary data tables that are focused on conventional pesticides (subparts C – O). Individual subparts are devoted to biochemical (subpart U) and microbial (subpart V) pesticides. The revised data requirements for antimicrobial pesticides would be incorporated into part 158 as subpart W.

C. Subpart W of Part 158

Subpart W is proposed to be a freestanding series of tables and regulatory text establishing specific data requirements for each scientific discipline for antimicrobial pesticides. EPA recognizes that antimicrobial uses are generally different from the uses more typically associated with conventional pesticides (e.g., agricultural outdoor uses) and therefore can have different combinations of exposure considerations. The use patterns and expected exposures typically determine the data requirements for any pesticide. Antimicrobial pesticides are no different in this regard from conventional, biochemical, and microbial pesticides.

The order of proposed subpart W mirrors that of the larger part 158: from product chemistry, to efficacy, to hazard/toxicity requirements (both human health and ecological toxicity), to exposure data requirements (application and post-application human exposures, and exposure to residues in food), and environmental fate requirements, which overlap human exposure through drinking water. Units V–XIV of this preamble describe the revisions to the current requirements. The proposed data requirement tables are comprehensive. Generally, the data requirements for each discipline are discussed separately, but the applicator and post-application exposure disciplines are discussed together in a single unit.

D. Clarifying How to Use the Data Tables

Part 158 subpart B contains a step-wise process to assist the applicant in determining the data needed to support its particular product. At this time subpart B is specific to the needs of conventional, and biochemical and microbial pesticides. The process needed for antimicrobials is no different. EPA is proposing certain clarifying changes to subpart B to specify the needs of antimicrobial pesticides. Specifically, EPA proposes to include antimicrobial use patterns in § 158.100 and a reference to the antimicrobial use site index that will be available on the EPA website.

While EPA is attempting to assist the applicant in subpart B, it is important to emphasize that it is the applicant's obligation under FIFRA to demonstrate that an individual product meets the standard under FIFRA and that of FFDCA. Accordingly, applicants are encouraged to consult with the Agency on the appropriate data requirements, as proposed here, as related to their specific product prior to and during the registration process.

EPA is continuing its current system of identifying the applicability of data requirements in the data tables. In essence, the data requirements illustrate the questions the registrant will need to answer about the safety of the pesticide product before the Agency can register it. Because of the variety of chemicals and use patterns, and because EPA must retain flexibility to tailor data requirements as appropriate, only qualitative descriptors are in the tables. Test notes provide more specific information on the applicability of specific data requirements.

The table descriptors NR (not required), R (required), and CR (conditionally required) should be viewed as a general presentation, indicating the likelihood that the data requirement applies. The use of R does not necessarily indicate that a study is always required, but that it is more likely to be required than not. For example, if the applicant wanted to apply his pesticide to apples, then crop field trials would be required almost always on apples. However, if the physical/chemical properties of the chemical did not lend themselves to the test, such as performing an inhalation test with a chemical that is a solid and has an extremely low vapor pressure, then a waiver might be granted. Generally test notes for R studies discuss any particular circumstances when the testing might not be required.

The use of CR means a study is less likely to be required. Triggers in the test notes indicate the circumstances under which the Agency has learned through experience that the information is needed. Although only an approximation, if percentages were to be assigned to indicate the need for a particular study, then R could be viewed as representing the submission of a study 50% to 100% of the time and CR would be up to 50%.

Thus, NR, R, and CR are used for convenience to make the table format feasible, but serve only as a general indication of the applicability of a data requirement. In all cases, the test notes referred to in the table must be consulted to determine the actual need for the data. Applicants are also encouraged to visit the Agency's website, entitled ''Data Requirements for Pesticide Registration'' (see *http://www.epa.gov/pesticides/regulating/data_requirements.htm*). Since it is not

possible to sufficiently delineate all circumstances in test notes, consultation with EPA is encouraged.

The table format includes a column heading entitled ''Guideline,'' which refers to the OPPTS (Office of Pollution Prevention and Toxic Substances) Harmonized Test Guidelines. Guideline numbers are provided as information/guidance to applicants. These Guidelines set forth recommended instructions and test methods for performing a study to generate the required data. Since these are guidance documents, the applicant is not required to use these Guidelines, but may instead seek to fulfill the data requirement by other appropriate means such as alternative test methods, submission of an article from open literature, or use of modeling. The applicant may submit a protocol of his own devising for the Agency to review. However, the OPPTS Harmonized Guidelines have been developed through a rigorous scientific process, including extensive peer review by the FIFRA Scientific Advisory Panel. Additionally, many of the Guidelines have been harmonized internationally. As such, they represent the recommended approach to developing high-quality data that should satisfy EPA's data needs for risk assessment.

E. The Nature of Changes to Requirements

Proposed subpart W does not differ greatly from the data requirements for conventional pesticides promulgated in October 2007. Where this proposal differs is in the explicit adaptation of those data requirements to antimicrobials. As previously discussed, antimicrobial uses were covered in the original (1984) part 158. However part 158 (now transitioned for antimicrobials as part 161) was developed primarily for agricultural pesticides. Since the use patterns which now appear in tables in part 161 are not specific to antimicrobials, often it has been difficult to discern directly from such tables the data requirements for certain antimicrobials. Without extensive consultation with and interpretation from the Agency, frequently it has been difficult for applicants to effectively use the tables to determine which data requirements apply to antimicrobials.

Today's proposal reflects the Agency's current needs for risk assessment of antimicrobials. Describing the antimicrobial data requirements in terms of use patterns specific to antimicrobial uses provides a clarity that should reduce the need for extensive consultations.

There are nine new data requirements for antimicrobials set out in this proposal. Two (developmental neurotoxicity and immunotoxicity) are the same new data requirements as promulgated in the final rule for conventional chemicals (72 FR 60934) (see Unit VIII). While photodegradation in soil studies have been routinely required for conventional chemicals, this study would be a new data requirement for wood preservatives (see Unit XII). Similarly, two new exposure data requirements (soil residue dissipation and non-dietary ingestion exposure) are today proposed for antimicrobials (see Unit IX.D).

Four new data requirements (activated sludge sorption isotherm study; ready biodegradability study; porous pot study; and modified activated sludge, respiration inhibition test) are proposed today for antimicrobials that are not included in the final rule for conventional pesticides. This is due to the nature of antimicrobial pesticides, which includes many down-the-drain uses, i.e. those discharged to public treatment systems, and is discussed in Units XII.B. and C.

Most screening-level environmental fate assessments would be performed using the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests. For wood preservatives, the results of the photodegradation in soil study may also be considered in the screening-level assessment. If the porous pot study is triggered based on the results of the ready biodegradability study, then those results would also be considered.

EPA notes that its proposed approach for performing a screening-level fate assessment could potentially result in the submission of higher-tiered studies. There are seven higher-tiered environmental fate studies, that could be triggered based on a weight-of-evidence evaluation of the results of the screening-level studies. For example, if the screening-level assessment were to indicate that a down-the-drain chemical would partition to sludge, soil, or sediment, then higher-tiered environmental fate studies such as the aerobic and anaerobic soil metabolism studies may be required. If the chemical would partition to water then higher-tiered ecotoxicity studies such as the fish early life stage may be required. Thus, the higher-tiered studies that could be triggered include both the environmental fate and ecotoxicity scientific disciplines.

While not a new data requirement, subchronic dermal testing of end-use products has not been routinely required and therefore would be considered a new testing requirement. The circumstances for requiring the testing is the same as for conventional chemicals. (See Unit VIII).

Each data requirement proposed in Units, VIII, IX, X, XII, XIII, and XIV is described as ''new,'' ''current practices,'' or ''existing.'' ''New'' means that the data requirement has never been required or has rarely been required on a case-by-case basis, and has not been routinely considered during the Agency's evaluation of the data needed for the purpose of risk assessment.

''Current practices'' encompasses the data that is typically required to register an antimicrobial pesticide product. This would include existing data requirements that are codified in part 161 as well as those that are not codified in part 161 and are now being proposed for codification in part 158, subpart W. It would also include any study that has been routinely required on a case-by-case basis, or any study that is routinely considered during the Agency's evaluation of the data needed for the purpose of risk assessment but is infrequently required because the triggers for that study are infrequently met.

''Existing'' requirements are a subset of ''current practices.'' This particular subset means that the data requirement is codified in part 161 and being transferred to part 158, subpart W either ''as is'' or with specified changes to the test notes, to the Rs, CRs, and NRs, or to the use patterns for which required. If there are proposed revisions to an existing data requirement, then clarifications on these proposed revisions are included in the preamble. Such revisions include proposing changes such as a change from conditionally-required to required, a change in the number of test species, or expanding the number of use patterns for which the test is required.

As previously discussed, there are frequently consultations to discern data requirements for certain of the antimicrobial use patterns. These consultations have led to general understandings as to the data required for a particular use pattern. For certain use patterns, all of the studies are considered to be the Agency's current practices. As an example, for the wood preservative use patterns, there is not a good fit to any of the part 161 use patterns in the tables and therefore the data needed to register a wood preservative is difficult to interpret from those tables. Given these circumstances,

EPA developed a series of requirements developed specifically for wood preservatives. These requirements are not codified in CFR, but the applicants understand that these are the data needed for wood preservatives and they routinely provide these studies to EPA.

F. Tiered Data Requirements

The Agency has organized the proposed requirements for antimicrobial pesticide products to support a tiered testing approach. Under such an approach the Agency prescribes a specific subset of ''lower tier'' studies that are conducted first. The results of this first- or lower-tiered testing are then used in conjunction with exposure data or other information to determine the need for more complex ''higher tier'' studies. The risk assessment must provide sufficient information to make the risk management decisions needed to register the product or establish a tolerance. This is a significant factor in the tiering process.

Data requirements have been tiered when EPA believes it can adequately conduct a risk assessment using a tiered approach. The conditions for ''triggering'' these higher tiered studies are specified in the test notes to the tables in proposed subpart W. A tiered data submission process is intended to allow the Agency to assess a pesticide's risk without requiring the applicant to conduct and submit studies that may not be needed for the regulatory decision. For certain chemicals, data from lower tiered requirements may be sufficient in and of themselves or in combination with other data to address the Agency's risk concerns without submission of higher tiered data requirements. In other cases, data from lower tiered requirements may indicate that higher tiered data need to be provided. The Agency expects applicants to consult with the Agency, as needed, to determine when submission of higher tiered data may be required.

The Agency has tiered the data requirements based on an understanding of the potential exposure for a specific use pattern. As an example, for toxicology studies used to support human health risk assessments, the high human exposure grouping specifies 19 toxicology studies as required at the lower tier. The low human exposure grouping specifies 13 toxicology studies as required. The Agency considered the frequency, duration, and/or magnitude of the exposure to determine the lower tier of toxicology testing requirements for both the high and low human exposure groupings.

For ecotoxicity data requirements, the Agency requires a first tier of required data for all antimicrobials regardless of the use pattern. The need for higher tiered data depends not only on the frequency, duration, or magnitude of the exposure, but also on the results of the first tier of the data.

Such a flexible approach allows EPA to require enough data, but not more than enough, to make the required safety finding. Such an approach is the same as that used for other pesticides; however, for antimicrobials the progression from lower to higher tier requirements may differ from that of conventional pesticides because the uses and expected exposures are different.

G. Impact of this Proposal on Future and Existing Registrations

This proposal concerns prospective data requirements for future registrations of antimicrobial pesticides. That is, these proposed data requirements, once final, would apply to all new applications for registration of antimicrobial pesticides submitted after the effective date of the rule. The new data requirements would also apply to applications of antimicrobial pesticides that are undergoing Agency review when the new regulation goes into effect. EPA believes that there may be a need for some type of a limited transition ''window'' for certain antimicrobial registration applications. EPA anticipates applicants of applications that were submitted, but not yet approved when the new regulations go into effect, may need to discuss with EPA the specifics of their application and whether additional time may be needed to complete generation of certain studies that may then be required to fulfill new data requirements. The Agency specifically requests comment on implementing the effective date of the final rule for antimicrobials with regards to future registrations of antimicrobials.

The Agency does not intend to apply these requirements automatically or routinely to all existing pesticide registrations. While EPA intends a flexible approach to imposing the new requirements upon existing products, the Agency may find it necessary to call-in data on certain existing registrations, for example, as warranted by emerging risks of concern for particular pesticides or as a result of possible future programmatic changes and priorities on existing pesticides, or during registration review.

However, EPA notes that issuance of this proposed rule provides notice to applicants of potential new data requirements and of potential expansion of existing data requirements to additional antimicrobial use patterns. Applicants and potential applicants for new registrations as well as registrants of existing products may wish to evaluate their products in light of the proposed requirements. As always, the Agency encourages applicants to consult with EPA, if they have any questions regarding data requirements.

H. Weight-of-Evidence Approach

The weight-of-evidence (WOE) approach is referenced in several subpart W test notes. Such an approach requires a critical analysis of the entire body of available data for consistency and biological plausibility. Some considerations in this approach are listed below:

- Sufficiency of data. Studies that completely characterize both the effects and exposure of the agent have more credibility and support than studies that contain data gaps.
- Quality of the data. Potentially relevant studies are judged for quality and studies of higher quality are given more weight than those of lower quality.
- Evidence of causality. The degree of correlation between the presence of an agent and some adverse effect is an important consideration.
- Corroborative information. Supplementary information relevant to the conclusions reached in the assessment is incorporated, e.g., studies demonstrating agreement between model predictions and observed effects.

WOE considers the kinds of evidence available, how that evidence fits together in drawing conclusions, and significant issues/strengths/limitations of the data and conclusions. WOE is not simply tallying the number of positive or negative studies.

I. Use Patterns in Subpart W

The general use pattern groups described in subpart B of part 158 are not used as the bases for describing antimicrobial data requirements. Those general use patterns were developed for and are appropriate to conventional pesticide chemicals.

Some years ago, 12 use categories were developed specifically for antimicrobials. At that time the Agency's data requirements for all pesticide chemicals were specified by use patterns developed for and appropriate to conventional pesticide chemicals. To fit antimicrobial uses into this agricultural scheme, the antimicrobial use categories referred back to the then-existing use patterns. With the Agency's intention to establish specific data requirements for

antimicrobials in subpart W, this referral is no longer needed.

Therefore, the Agency is proposing that the use categories employed in recent years to generalize the range of uses for individual antimicrobial pesticide chemicals, now constitute the use patterns for specifying the antimicrobials data requirements in the tables in proposed subpart W. Additionally, EPA is proposing to codify in § 158.2201 the specific use patterns for antimicrobials.

FIFRA section 3(h)(3)(A)(ii)(I) requires that EPA ''define the various classes of antimicrobial use patterns.'' For antimicrobial pesticides, the Agency proposes to structure its requirements by using a system of 12 use patterns based on similarity of use, purpose, pesticidal function, the nature of the exposure, and, in some cases, application methods. Today's proposal meshes with the statutory mandate to identify classes of antimicrobial use patterns by defining for each use pattern the data requirements that apply. EPA requests comment not only on the 12 antimicrobial use patterns described in this Unit, but also on the usefulness of these use patterns. EPA also requests comment on whether or not any different/additional use patterns should be codified by splitting or recombining the existing use patterns to make separate and distinct use patterns.

Antimicrobial use patterns also reflect environmental concerns for indoor versus outdoor use, as well as food versus nonfood-use, and high versus low human exposure. The 12 general use patterns for antimicrobial pesticides are described below. Examples within each use pattern are provided:

1. *Agricultural premises and equipment*. This use pattern includes many indirect food uses with mostly indoor use sites.

- Farm and farm animal premises such as animal houses and pens (including milk houses), parlors, stalls, and barns.
- Transportation vehicles used to transport animals.
- Equipment such as forks, shovels, scrapers; halters, ropes, other restraining equipment; racks, mangers, feeders, waterers, troughs, and fountains.
- Food-handling equipment such as milking equipment.

2. *Food-handling/storage establishments, premises, and equipment*. This use pattern also includes many indirect food uses due to the treatment of food contact surfaces and the resultant human exposures. All use sites are indoor.

- Food or feed processing plants.
- Eating establishments such as restaurants and cafeterias.
- Food storage or distribution facilities.
- Commercial transportation vehicles, shipping, and storage containers.
- Food or feed stores and markets.
- Vending machines.

3. *Commercial, institutional and industrial premises and equipment*. This use pattern includes nonfood contact areas of commercial sites. Typically, antimicrobial pesticides would be applied to ceilings, doors, doorknobs, fixtures, floors, light switches, stairs, walls, windows, and woodwork as part of routine cleaning practices. Included within this use pattern are residential school and daycare institutions.

This use pattern includes both indoor and outdoor uses. Some of the uses have the potential for significant exposure due to the repetitive nature of certain exposures and therefore may be considered as high human exposure.

4. *Residential and public access premises*. This use pattern includes mostly nonfood areas, although it includes food-handling areas in homes. Some of the uses have the potential for significant exposure due to the repetitive nature of certain exposures and therefore may be considered as high human exposure. Most uses are indoor.

- Premises, contents, and equipment of homes, apartments, mobile homes and shelters, including home-based daycare.
- Public areas, public buildings, and public rooms.
- Commercial kennels, or living quarters of pets, zoo animals, race horses, or laboratory animals.

5. *Medical premises and equipment*. Medical waste is defined as any solid waste that is generated in the diagnosis, treatment, or immunization of human beings or animals, in research pertaining thereto, or in the production of biologicals including, but not limited to, culture and stocks, pathological wastes, human blood and blood products, and sharps. This use pattern is considered to be indoor nonfood. Some of the uses have the potential for repeated exposure and therefore may be considered as high human exposure.

- Hospital or medical environments such as clinics, dental offices, nursing homes, sick rooms, morgues, and veterinary clinics.
- Non-critical medical equipment such as bedpans, basins, and furniture.

6. *Human drinking water systems*. Human drinking water systems include any methods used to provide potable water from raw water supplies. This use pattern is considered to be high human exposure due to the potential for human exposures via drinking water, as well as dermal exposures to the treated water.

- Public water systems.
- Individual water systems.
- Emergency water systems.
- Water purifier units.
- Private water systems of individual homes, farms, institutions, camps, resorts, and industrial plants.
- Emergency water systems for the public, campers, travelers, military, and fishermen.

7. *Materials preservatives*. Materials preservatives are antimicrobial chemicals added during industrial processes to prevent the growth of microorganisms. Examples of such uses include paints, coatings, adhesives, textiles, and paper. This use pattern includes food and nonfood, and mostly indoor uses.

8. *Industrial processes and water systems*. Certain antimicrobial chemicals, known as microbiocides, are used to control the growth of bacteria, fungi, and algae in circulating water systems. There are two types of systems: ''once-through'' and ''recirculating.''

For ''once-through'' systems, the water is not re-used and is therefore released into the aquatic environment or a wastewater treatment plant after a single cycle through the system. Once-through uses have the potential for significant environmental exposure when the treated water is released to the environment. Large volumes of water (as much as millions of gallons per minute) may be released directly to a river, estuary, or marine environment within minutes or hours of adding the antimicrobial to the system. In addition to the potential for environmental exposure after release, there is the potential for high human exposure via drinking water if the intake pipe for a drinking water treatment plant is downstream. Also, the water could be used in crop and/or livestock production thus providing for additional human exposure.

However, for many uses of water in industrial plants the treated water is re-used repeatedly within the system, ''recirculating'' in the system multiple times until released into the aquatic environment or a wastewater treatment plant. EPA has assumed that the releases are scheduled as the antimicrobial has been ''used-up.'' Given the lower frequency of release, resulting in lower volumes released to the environment, recirculating uses are likely to have less environmental exposure than that of once-through systems.

As will be explained later in Unit XI, for the purposes of determining data requirements for environmental fate and

ecological effects, the industrial processes and water systems use pattern will be subdivided. Because of the distinct differences between the once-through and recirculating water systems, the once-through water system will be grouped with those use patterns with potential for higher environmental exposures and the recirculating water system with those use patterns with the potential for lower environmental exposures.

9. *Antifoulant paints and coatings*. Antifoulants are coatings and paints applied to boat hulls and bottoms, crab and lobster pots, and underwater structures or equipment to control the growth of freshwater or marine fouling organisms. Antifoulant coatings have the potential for high environmental exposure most particularly for marine (both freshwater and saltwater) environments.

Also included within this use pattern is ballast water, that is, the water that is pumped in and out of ballast tanks as a ship's weight changes due to loading and unloading of cargo. Ballast water provides needed stability for safe operation of marine vessels. In recent years there have been significant concerns about transport of marine species from one marine environment to another in ballast water. When discharged into a new environment, the new species may become invasive and disrupt the native ecology. Ballast water treatments (such as adding an antimicrobial to the ballast water before discharge) are intended to prevent this. The Agency has reviewed few applications for ballast water treatments, presumably because treatment of ballast water to prevent the transfer of microorganisms from one marine environment to another is relatively new. Since ballast water treatments also have the potential for high exposure to the aquatic (both freshwater and seawater) environment, EPA has grouped the ballast water treatment pesticide chemicals with the antifoulant coating pesticide chemicals.

10. *Wood preservatives*. Wood preservative products are those which claim to control wood degradation problems due to fungal rot or decay, sapstain, molds, or wood-destroying insects. This use pattern has the potential for high exposure for both humans and the environment with mostly outdoor use sites. Certain uses can be food-uses. The types of wood and the products that can be manufactured with this treated wood are:

- Freshly cut logs or lumber.
- Seasoned building materials.
- Utility poles, fence posts and rails.
- Structural members.
- Structures and dwellings.
- Transportation vehicles (truck beds and support structures).
- Crop containers.
- Lawn furniture and decks.
- Playground equipment.
- Garden/landscape timbers.
- Log homes.

11. *Swimming pools*. Products in this use pattern are used to prevent/control the growth of bacteria or algae in the water systems of swimming pools, Jacuzzis, and hot tubs. This use pattern is considered to be high human exposure. Under routine use little or no environmental exposure is expected, as the water in swimming pools, Jacuzzis, or hot tubs is considered to be separated from the natural environment. However, when draining is needed, depending on the volume of water and the location of the pool or hot tub, it is most likely that discharge would be down-the-drain to a wastewater treatment plant, to a storm drain that discharges to a stream, or directly to soil.

12. *Aquatic areas*. Products in this use pattern are designed to control or kill slime-forming bacteria, fungi, or algae in lakes, ponds, streams, drainage ditches, and other bodies of water. In addition to the potential for environmental exposure, there is the potential for high human exposure via drinking water if the intake pipe for a drinking water treatment plant is in a lake or downstream, or through recreational activities such as swimming. Also, the water could be used in crop and/or livestock production thus providing for additional human exposure.

J. Use Site Index

As part of this action, the Agency is proposing to place on its website an Antimicrobial Use Site Index similar to the existing Pesticide Use Site Index at *http://www.epa.gov/pesticides/regulating/usesite/index.htm*. Information similar to that which would be included on the Antimicrobial Use Site Index is included in the docket for this action (Ref. 41). The existing Pesticide Use Site Index will be re-titled, the Pesticide Use Site Index for Conventional, Biochemical, and Microbial Pesticides to distinguish it from the Antimicrobial Use Site Index.

K. Request for Comments

The Agency invites the public to provide its views and suggestions for changes on all of the various proposals in this document. Specifically included within the Agency's request for comments are the following proposals:

- SAR white paper.
- Four case studies.
- 12 general use patterns, suggestions for different/additional use patterns, and their utility.
- Proposed new down-the-drain requirements.

Additionally, in other parts of this proposed rule, EPA is specifically requesting comments on certain issues.

As appropriate during the development of this proposal, EPA has occasionally shared information with the regulated community on the data requirements that were under consideration. Commenters are encouraged to comment on such sharing of information as part of the administrative process of developing this proposed rule.

The Agency welcomes comments on the following topics of particular interest to the Agency:

- All aspects of the administrative process used to develop this proposed rule including outreach activities.
- The need for, value of, and any alternatives to, the data requirements described in this document.
- The scientific basis of this proposed rule.
- The clarity of the proposed data requirements for antimicrobial pesticides and the relationship between the proposed data requirements and EPA's statutory determinations.
- The economic analysis of the proposed rule, as well as on its underlying assumptions, economic data, and high- and low-cost options and alternatives.

Commenters are encouraged to present any data or information that should be considered by EPA during the development of the final rule. Describe any assumptions and provide any technical information and data used in preparing your comments. Explain estimates in sufficient detail to allow for them to be reproduced for validation. EPA's underlying principle in developing the proposed revisions has been to strike an appropriate balance between the need for adequate data to make the statutorily mandated determinations and informed risk management decisions, while minimizing data collection burdens on applicants.

V. Product Chemistry

The Agency proposes to apply the product chemistry data requirements for conventional pesticide chemicals, in subpart D, to antimicrobial products. These requirements were promulgated in the final rule on October 26, 2007, (72 FR 60934). Product chemistry requirements identify the basic identity, and chemical and physical characteristics of a pesticide chemical.

These data, to a limited extent, are used to determine if a pesticide contains contaminants which are of toxicological or environmental concern and are necessary to determine proper label precautions. Product chemistry requirements are generally not dependent on a pesticide's intended use pattern, and therefore it is appropriate to apply the same requirements to antimicrobial pesticides as required for conventional pesticides. If circumstances particular to antimicrobial pesticides should arise, then the Agency has the authority to require the appropriate product chemistry data on a case-by-case basis.

VI. Product Performance Data Requirements

EPA is not proposing to revise product performance data requirements (§ 158.2220) at this time. At this time there are nearly identical product performance data requirements for antimicrobial chemicals in both § 158.400 and part 161. EPA proposes to transfer the contents of the existing product performance data requirements for antimicrobial pesticides into subpart W, specifically § 158.2220. The table is transferred essentially unchanged. EPA is also proposing to delete the duplicative data requirements for antimicrobials from the table in § 158.400. After the publication of the final rule, all product performance data requirements for antimicrobials will be contained in § 158.2220.

In the **Federal Register** of September 17, 1999, (64 FR 50726), EPA published a proposed rule entitled, ''Registration Requirements for Antimicrobial Pesticide Products and Other Pesticide Regulatory Changes.'' In that proposed rule, EPA proposed various definitions for public health pesticides. Today, the Agency is re-proposing definitions for the following terms: disinfectant, fungicide, microbiological water purifier, sanitizer, sterilant, tuberculocide, and virucide. These proposed definitions are identical to those in the 1999 proposal. The Agency is also re-proposing the 1999 criteria that EPA would use to consider whether a product makes a public health claim. The comments that were received on the 1999 proposed rule were considered for today's proposed rule.

The current regulations in part 161 require that each applicant must ensure through testing that its products are efficacious when used in accordance with label directions and commonly accepted practices. The requirement to submit product performance data is directly linked to making a public health claim. Today's proposal makes explicit what antimicrobial claims would be considered public health claims for purposes of product performance data submission.

At the time of application, EPA requires the submission of product performance data for products making a public health claim. An application will not be approved in the absence of acceptable data substantiating a public health claim. EPA requires the development of product performance data for all other (non-public–health) products, but does not review or approve such data as part of a new or amended registration. If, after the product has been registered, EPA has reason to review such data (for example, there are indications that the product does not perform as claimed), then EPA will require the registrant to submit such data within a reasonable time. A request for submission of product performance data after product registration is not required to be done under the Data Call-In provisions of FIFRA section 3(c)(2)(B), but is instead authorized by regulation.

Accordingly, if an antimicrobial product makes a claim to control microorganisms that pose a threat to human health, the applicant is then required to submit product performance data to support its registration. The types of product performance data required by the Agency to support registration of an antimicrobial are determined by the types of claims made on the product's label (e.g., sanitizer, disinfectant) and the intended use site for the product (e.g., hard surface, fabric).

VII. Human Health Risk Assessment

The data needed to conduct a human health risk assessment include both toxicology and exposure data. Toxicology studies are used to assess hazards of pesticides to humans and domestic animals, and include a variety of acute, subchronic, and chronic toxicity studies; developmental/reproductive tests; and tests to assess mutagenicity and pesticide metabolism. To assess human health risk, there must be sufficient information to select the appropriate doses and end-points, i.e., the Agency must know the level of exposure at which an adverse effect is observed. This requires a toxicological database that is not only complete in the endpoints it covers, but is also of acceptable quality. The duration of the toxicity study approximates the estimated duration of the human exposure, while considering species differences in maturational milestones and overall life span. The toxicology data requirements are discussed in Unit VIII of this preamble.

For EPA to assess the potential risks that antimicrobial products pose to humans, it is necessary not only to assess the hazard of the antimicrobial active ingredient based on toxicology information, but also to estimate human exposures to the antimicrobial based on the product use patterns. For antimicrobials, three types of exposure data are required: applicator, post-application, and residue chemistry (which includes exposure via food and water).

Applicator and post-application exposure data are used to evaluate exposures to persons in occupational and non-occupational settings, including residential, commercial, institutional, and recreational sites. Exposure data include: dermal and inhalation exposure data for applicators, post-application residue data, post-application monitoring data, use information, and human activity information. Applicator and post-application data requirements are discussed in Unit IX of this preamble.

Residue chemistry information is used to establish tolerances for residues of pesticide chemicals (and any metabolites of concern) in/on food crops, processed foods, and animal products consumed by humans when the animal consumes a feed item derived from these crops. The Agency estimates the dietary exposure of the general population and various population subgroups to pesticide residues in food by using the residue data as inputs to the dietary modeling. The dietary exposure is then used in conjunction with toxicity data to determine risk. Residue chemistry data requirements are discussed in Unit X.

VIII. Toxicology Data Requirements

A. Toxicology Data Requirements for Antimicrobials

EPA proposes to adapt the basic toxicology data types as listed in subpart F of current part 158 to support applications for antimicrobial products. However, EPA also proposes to modify the applicability of those requirements to reflect the differing risks of and levels of exposure to antimicrobials.

As with conventional pesticides, the types of toxicology studies required for antimicrobials can include acute, subchronic, and chronic toxicity studies, as well as carcinogenicity, prenatal developmental toxicity, reproductive toxicity, mutagenicity, neurotoxicity, immunotoxicity, and other studies.

1. Acute toxicity studies provide information that serves as a basis for classification and precautionary labeling and the need for child resistant packaging.

2. Subchronic toxicity studies provide information that can be used to assess human health hazards that may result from repeated exposures to a pesticide over a limited period of time. These data also provide information for selecting proper dose levels for chronic/carcinogenicity studies.

3. Chronic toxicity studies are used to assess potential hazards resulting from prolonged and repeated exposures to a pesticide over a significant portion of the life span.

4. Prenatal developmental toxicity studies are designed to assess the potential of a pesticide to induce effects in offspring as the result of exposure of the mother during pregnancy.

5. Multigeneration reproduction studies are designed to provide information concerning the general effects of a pesticide on overall reproductive capability.

6. Mutagenicity studies assess the ability of the pesticide to interact directly or indirectly with cellular DNA, RNA, proteins, or chromosomes and the potential for adverse effects on cellular genetic material.

7. Neurotoxicity studies evaluate the potential of the pesticide to adversely affect the structure and functions of the nervous system.

8. Immunotoxicity studies evaluate the potential of the pesticide to adversely impact the immune system.

9. Metabolism studies evaluate the absorption, distribution, biotransformation, and excretion of the pesticide.

B. The History of Toxicology Requirements for Antimicrobials

By 1984, the Agency had reconsidered its toxicology data requirements for all pesticides, including antimicrobials. For instance, it had become clear that exposure to antimicrobial pesticides might well be long-term and frequent since many antimicrobials were used indoors in close proximity to humans. Occupational users often were exposed to concentrated antimicrobial products while mixing and diluting the product for use, and might be exposed to an antimicrobial pesticide for large portions of their working lifetimes. In response to the reregistration program initiated under the 1988 amendments to FIFRA, EPA concluded that additional data were needed to properly evaluate the potential hazards associated with antimicrobial pesticides. Consequently, the Agency began to require more toxicity data for antimicrobials. In 1987, based on its evolving understanding of antimicrobial uses, the Agency issued an Antimicrobial Toxicology Data Call-In (DCI) Notice (52 FR 595, January 7, 1987) (Ref. 24), which specified a tiered approach for submission of toxicology and human exposure data.

The 1987 Antimicrobial Toxicology DCI divided antimicrobial pesticides into three exposure categories: low, medium, and high. The toxicology data required was tiered according the amount of exposure. The first tier toxicology data requirements (low exposure) were the standard acute studies, a 90–day dermal or inhalation study, a prenatal developmental toxicity study in one species, and a battery of mutagenicity studies. The second tier (medium exposure) included the first-tier toxicology studies and a subchronic feeding study, a prenatal developmental study in a second species, and a dermal absorption study. The third tier (high exposure) included the first- and second-tier studies and the chronic feeding, carcinogenicity, reproduction, and metabolism studies. All food-use antimicrobials were considered high exposure.

Applicants could fulfill the toxicology data requirements by submitting the appropriate toxicity studies or by submitting a combination of toxicity studies and exposure data. The Agency used the exposure data and submitted toxicology data to determine whether and which additional toxicology studies were needed to assess the hazard of the antimicrobial.

In proposing part 158, subpart W, the Agency is specifying the toxicology data requirements it believes are appropriate for specific antimicrobial use categories, drawing upon EPA's experience since 1987. EPA is now proposing two groupings: Low- and high-exposure. In practice, the submission, review, and evaluation of toxicity data merged the low- and medium-exposure categories. Therefore, the low- and medium-exposure categories from the 1987 DCI were combined to create what is today the low exposure category.

Today's proposed approach conceptually follows the tiering approach used in 1987. Generally, data requirements proceed in a tiered manner from simpler to more complex studies considering the frequency, duration, and magnitude of exposure as well as the dermal absorption of the pesticide. Knowledge gained from results of assessments performed using these lower tiered studies is used to indicate if any higher tiered studies are required. The Agency does not prescribe a required sequence of toxicological testing. There are many factors that could affect the testing progression. Rather, decisions regarding the sequence in which the tests are conducted are left up to the applicant. Thus, the applicant has flexibility to determine the sequence of testing, as best suited for their particular chemical. Early consultation with the Agency is recommended to attain a common understanding of the sequencing that should be used.

C. Groupings for Antimicrobial Toxicology Data Requirements

1. *Overview*. This proposal divides the antimicrobial uses into two groups, high human exposure and low human exposure uses. Because high human exposure uses may pose higher risks, more toxicology studies are required than for uses with less exposure. For the purpose of determining toxicology data requirements, high human exposure is defined as that resulting in human exposures over a considerable portion of the human lifespan. Exposure to food and water, which occurs throughout the human life span, is therefore a high human exposure. For other exposures such as occupational and residential, the Agency has considered the frequency, duration, or magnitude of the exposure to determine in its best professional judgment if the exposure is high. One or a combination of these parameters led the Agency to make the determination that the exposure is high. As an example, swimmers may swim daily or weekly, from several minutes to several hours with almost their entire body in the water. There are workers who manually pour concentrates into vessels for mixing (with water or other chemicals) in order to prepare dilute solutions for use. Such exposures can occur daily, weekly, monthly, or episodically as dictated by the circumstances of the job. Particularly in the absence of personal protective equipment, these workers have the potential for high dermal and inhalation exposures. Accordingly, for the purposes of defining data requirements, EPA proposes to categorize food and feed uses and certain nonfood-uses as high human exposure.

As discussed, the Agency considers high human exposure uses to be those that could result in pesticide residues occurring in food or feed, or in drinking water. These would include, but are not limited to:

- Human or animal drinking water.
- Fruit and vegetable rinses.
- Egg washes.
- Outdoor aquatic uses in lakes, rivers, or streams which have the potential to contaminate potable water.

• Indirect food uses with residues equal to or greater than 200 parts per billion (ppb).

• Any use that requires a tolerance or tolerance exemption (except for indirect food uses requiring a tolerance or tolerance exemption in which residues are less than 200 ppb).

EPA also considers high human exposure uses to be those uses that could result in high exposure to applicators, and any other antimicrobial uses which could result in high exposure to humans. These would include but are not limited to:

• Wood preservatives.

• Metal cutting (metalworking) fluids.

• Swimming pools.

This list is not exhaustive. There may be other uses that the Agency would consider high human exposure uses based on their potential for human exposure. Low human exposure uses are defined as those that are not high human exposure uses.

The Agency is proposing an approach that might allow an applicant for registration of a pesticide with low human exposure uses to generate fewer studies in total than would be required for high human exposure uses. Under this proposal, applicants with low human exposure antimicrobials may perform tests in a tiered fashion. As previously explained, for toxicology studies the high human exposure grouping specifies 19 toxicology studies as required, and for the low human exposure grouping, 13 toxicology studies as required. After the 13 required studies for low human exposure are reviewed by the Agency, additional testing may be required for low-exposure uses based on the result(s) of the lower-tiered studies. These 13 studies could indicate a low risk potential or could trigger the need for additional data.

The table in proposed § 158.2230 presents the toxicology data requirements. The proposed toxicology data requirements for the two groupings (high human exposure and low human exposure) are separated into two columns showing test by test whether it is typically required (shown as R) or conditionally required (shown as CR).

The Agency recognizes that toxicology testing can represent a large burden on applicants and can involve significant animal testing. Consequently, the Agency works with applicants, the scientific community, and other stakeholders to ensure that data requirements produce the information needed to enable the Agency to make the safety findings required under FIFRA and FFDCA. The tiering process proposed within the toxicology data requirements requires fewer studies for lower exposures. The Agency also works to design study protocols that minimize the development burden and limit uses of test animals. Toxicity testing requirements may be satisfied in a combined study, such as combining the prenatal developmental and reproductive toxicity testing requirements in a single study. However, if this option is chosen, the protocol must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

2. *Data requirements for high human exposure uses.* For high human exposure uses, EPA is proposing to require the following studies: Acute oral, dermal, and inhalation toxicity; primary eye and dermal irritation; dermal sensitization; subchronic studies in two species; mutagenicity studies; acute and subchronic neurotoxicity testing; prenatal developmental toxicity studies in two species; a two-generation reproduction study; a chronic feeding study in one species; carcinogenicity studies in two species; a mammalian metabolism study; and an immunotoxicity study. Based on a weight-of-evidence evaluation, a developmental neurotoxicity study may be required. If the Agency determines, based on use information that dermal exposure is the major route of exposure, then EPA may require dermal absorption testing or toxicological studies conducted by the dermal route.

i. *Wood preservatives.* For wood preservatives, the Agency may require toxicity data on both the active ingredient which is incorporated into the wood and on transformation/degradation products which occur in wood post-treatment. Such transformation/degradation products would include dislodgeable residues (i.e., residues that occur from hand contact with treated wood) or leachate residues (i.e., residues that occur in soil or water in contact with treated wood).

ii. *Metal working fluids (MWFs).* While both ''open'' and ''closed'' MWF systems are high human exposure uses, under the appropriate circumstances, the Agency distinguishes between ''open'' and ''closed'' systems. Fewer toxicity data may be required for a ''closed'' system. If the use of the MWF is limited to ''closed'' systems only, the applicant clearly identifies the use as such, and the Agency agrees, then fewer toxicity studies would be required for that ''closed'' system. Based upon review and evaluation of the submitted toxicity studies and exposure data, EPA may determine that fewer additional toxicity studies than would generally be submitted are required. Upon request the Agency will provide written guidance concerning exposure, toxicity, and other data requirements for ''open'' and ''closed'' MWF systems.

3. *Data requirements for low human exposure uses.* As previously discussed, the Agency proposes to apply a tiered system to toxicology testing requirements for low human exposure antimicrobials. The required data are: Acute oral, dermal, and inhalation toxicity; primary eye and dermal irritation; dermal sensitization; a subchronic toxicity study in the rodent; prenatal developmental toxicity studies in two species; a two-generation reproduction study; mutagenicity studies; and immunotoxicity testing.

Based on the review of these studies, additional studies may be required if there is evidence of significant toxicity in the submitted studies. Evidence that could trigger concerns may include data indicating neurotoxicity, immunotoxicity, developmental, reproductive, or other systemic toxicity such as the presence of neoplastic growth or significant target organ toxicity. In such cases, appropriate studies to address the Agency's hazard or risk concern would be required. The table in proposed § 158.2230 contains test notes that explain how these toxicology requirements are proposed to be applied to low human exposure antimicrobials.

4. *Data requirements for indirect food uses.* For the purpose of determining toxicology data requirements, an antimicrobial use is considered an indirect food use when the antimicrobial pesticide is applied to a surface or incorporated into a material that may contact food, but is not applied directly to food. Residues of the pesticide or its degradates can be transferred to the food when it comes into contact with these treated surfaces and articles. Examples of antimicrobial uses which may result in residues in food, through normal use, are sanitizers and disinfectants, which may be used in food-handling areas, but not directly applied to the food.

With the passage of the Food Quality Protection Act of 1996 (FQPA), as later modified by the Antimicrobial Regulation Technical Corrections Act of 1998 (ARTCA), EPA currently has the responsibility for establishing tolerances or tolerance exemptions for all pesticide uses that result in residues in or on food, except for:

• Residues that result from the use of antimicrobial substances on food or in water that comes into contact with food, if such substances are used where food

is prepared, packed, or held for commercial purposes. (For raw food commodities, this exclusion does not apply if the antimicrobial is applied in a facility where only such foods are treated and the treatment of the foods does not constitute food processing.)

• Antimicrobial substances used as food contact substances in or on food, such as those used in the manufacture of food contact packaging. This exclusion does not apply to objects impregnated with a food contact substance (other than food packaging material) if the inclusion of the substance is intended to have an antimicrobial effect on the food contact surface of the object.

FDA has the responsibility for regulating these antimicrobial substances as food additives under section 409 of the FFDCA. However, under the provisions of FIFRA section 2(bb) prior to registration of a pesticide that may result in residues of that pesticide in or on food (including sanitizers, disinfectants, and slimicides), EPA must make a safety finding that the pesticide residue meets the standard set forth in section 408 of FFDCA. This applies even if FDA will establish a food additive regulation for the use of the antimicrobial substance under section 409 of the FFDCA.

Since publication in 2002 of its final guidance for toxicology recommendations for food contact substances, FDA has used an approach with several tiers: residues less than 0.5 ppb, between 0.5 and 50 ppb, between 50 ppb and 1,000 ppb, and greater than 1,000 ppb. EPA recognizes the historic usefulness of the FDA's tiered approach and proposes to adopt it conceptually, but with a modification appropriate to antimicrobials (biocides). FDA's guidance (Ref. 8) specifically recommends that a factor of 5 be used to account for the toxicity of biocides. Further modifications to this approach are needed for EPA to perform an assessment of risk that conforms to the FFDCA section 408 safety finding which now requires consideration of the ''... special susceptibility of infants and children to the pesticide chemical residues....''. Thus, additional studies are needed even for the lower exposures for which FDA historically would not have required data.

Accordingly, EPA proposes to classify indirect food uses of antimicrobials which result in residues in or on food of less than 200 ppb as low human exposure uses for purposes of subpart W. Given FDA's historical experience with biocides, EPA believes that the 200 ppb (1,000 ppb divided by 5) benchmark is a reasonable delineation between high and low human exposures. Antimicrobials used in a manner which results in residues in food from an indirect use that are equal to or greater than 200 ppb would be considered high exposure uses. The Agency specifically requests comment on the use of 200 ppb residues in food as the differentiation between the high and low human exposure for the purposes of subpart W.

For indirect food uses, the applicant should begin the process by collecting all available information. Since many indirect food uses were previously evaluated by FDA, there may be a petition that was submitted to FDA. For some chemicals, toxicity testing may have been conducted and reviewed in the open literature. After identifying the available reliable information, the applicant should compare this information to the data requirements in the appropriate column in the table in § 158.2230. If the applicant believes that an existing study satisfies the data requirement, then this should be discussed with EPA.

The applicant is also encouraged to review the approach discussed in Unit XVIII.A. of this preamble on the use of Structure-Activity-Relationship (SAR) assessments to ascertain if such techniques could provide useful information in preparing a submission to EPA.

D. Acute Toxicity Studies for End-Use Products

EPA proposes to add a test note to clarify that the currently required six acute toxicity studies are to be conducted on the product as formulated for sale and distribution. These six acute studies may also be needed for the product as diluted for use. Many antimicrobial products are diluted at the point of use, but can still lead to significant exposure. The applicant has the option of also conducting certain studies using the highest diluted concentration (i.e., the least diluted product) permitted by the labeling. This test note codifies EPA's current practices. Consultation with the Agency is highly suggested to assure that the appropriate product and any appropriate dilutions are tested.

E. Neurotoxicity

EPA promulgated toxicity requirements for conventional pesticide chemicals, in which the data requirements for neurotoxicity were revised. The former test battery of three studies was revised to include only two studies. The rationale for those revisions was discussed in Unit XI of that proposed rule (March 11, 2005) (70 FR 12276), and in the final rule preamble (October 26, 2007) (72 FR 60934). That rationale is also applicable to antimicrobial pesticide chemicals.

EPA proposes to adopt the current conventional pesticide data requirements for neurotoxicity testing to antimicrobials. Adopting the battery of two neurotoxicity studies would codify the Agency's current practices.

The current adult neurotoxicity test battery for antimicrobials in part 161 consists of three studies: Acute delayed neurotoxicity (hen), 90–day neurotoxicity (hen), and 90–day neurotoxicity (mammal). The mammal subchronic neurotoxicity study is required if the acute oral, dermal, or inhalation toxicity studies show neurotoxicity or neuropathy. The existing required data are inadequate for evaluating neurotoxic effects of some chemicals.

The proposed battery of two studies in the rat is more sensitive than the neurotoxicity tests currently required in part 161. The objective of the proposed acute and subchronic neurotoxicity battery is to evaluate the incidence and severity of the functional and behavioral effects, the level of motor activity, and the histopathology of the nervous system following exposure to a pesticide chemical.

Under this proposal, an adult neurotoxicity test battery of two studies would replace the current battery of three studies. The two studies are an acute and a subchronic 90–day neurotoxicity study in rats. The acute study would detect possible neurotoxic effects resulting from a single exposure. The subchronic study would detect possible effects resulting from repeated exposures. These studies were presented to the FIFRA SAP in 1994, which endorsed them, and the Agency has generally required them on a case-by-case basis since 1992 for all pesticides, including antimicrobial pesticides.

The required parameters for a subchronic neurotoxicity study may be incorporated into the standard 90–day subchronic feeding study in rats. The acute and subchronic neurotoxicity studies in adult rats, in addition to providing data on the potential for adverse neurotoxic effects, may also provide a basis for comparing the potential for age-related differences in impacts on the nervous system if a developmental neurotoxicity study is triggered for the same chemical.

For high human exposure uses, EPA proposes to require both the acute neurotoxicity and subchronic neurotoxicity studies in the rat. For low human exposure uses, both

neurotoxicity studies are proposed to be conditionally required (CR) and would be triggered if there is evidence of neurotoxic effects in the 90–day oral study in rodents or if other data show evidence of neurotoxicity.

F. 90–Day Oral Studies

EPA proposes to adopt the current conventional pesticide data requirements for subchronic (90–day) studies to antimicrobials. Oral 90–day toxicity studies in two species are currently required in part 161 for high human exposure uses and conditionally required in part 161 for low human exposure uses. The Agency is proposing to continue this existing requirement for high human exposure uses in part 158, subpart W. The Agency is proposing to require an oral 90–day study in one species (rodent) for low human exposure uses and to conditionally require testing in a second species (non-rodent). For low human exposure uses, this change from two conditionally required studies to one required and one conditionally required study would codify current practices.

Often, range-finding studies of at least 90 days are needed to select the appropriate dose levels for the mouse carcinogenicity study. Thus, 90–day studies are often performed routinely by most investigators prior to the initiation of the carcinogenicity study. Often the range-finding studies have been submitted to the Agency for review. Because of their utility in determining the dose levels in the mouse carcinogenicity study, in the test notes, the Agency encourages the use of range-finding studies in the mouse.

Additionally, all 90–day subchronic studies in the rodent can be designed to simultaneously fulfill the requirements of the 90–day neurotoxicity study by adding separate groups of animals for testing. Although the subchronic guidelines include the measurement of certain neurological endpoints, they do not meet the requirement for a 90–day neurotoxicity study.

G. 21/28–day Dermal and 90–day Dermal Testing with End-Use Product

Currently in part 161 there is a conditional requirement for 21–day and/or 90–day dermal toxicity studies for all use patterns. The Agency is proposing to continue to conditionally require 21/28–day and/or 90–day dermal toxicity studies for all antimicrobials. As determined by the Agency, based on the use pattern, frequency of exposure, and magnitude of exposure, the 21/28 day study may provide the appropriate information for risk assessment purposes.

Just as with conventional pesticides, the Agency is proposing to require subchronic dermal testing of the end-use product if the product or any component of the product may increase dermal absorption of the active ingredient(s) or could potentiate toxic or pharmacologic effects. Testing of an end-use (formulated) product in either of these studies has not been routinely required and therefore would be a new testing requirement for antimicrobials. A test note has been added to both of these existing data requirements to describe the triggers for end-use product testing.

Currently, end-use products are required to be tested for acute dermal toxicity and dermal irritation. Without additional subchronic testing of the end-use product, risk from dermal exposure to an end-use product may be underestimated for those products that contain an inert ingredient that increases the dermal absorption of the active ingredient. An example of such an inert ingredient would be dimethyl sulfoxide.

H. 90–day Dermal and 90–day Inhalation Testing for HVAC&R Uses

Heating, ventilation, air conditioning, and refrigeration systems (collectively referred to as HVAC&R) refer to systems which refrigerate, exclusively air condition, or exclusively heat, as well as those in which one system provides both heating and cooling. HVAC&R systems are present in industrial, institutional, commercial, and residential establishments, and include, but are not limited to: air ducts, duct fittings, duct liners, fans, supply ducts, return ducts, exhaust ducts, intakes, outlets, louvers, diffusers, dampers, plenums, outdoor air intakes, air handling units, and any other ductwork and similar components. The Agency is concerned with potential exposures and risks from application of antimicrobial pesticide products used to treat the surfaces of HVAC&'s system components. An example of such treatment would be use of an antimicrobial as part of air duct cleaning.

HVAC&R is a unique use site which must be specifically identified on the label of the antimicrobial product. The application of an antimicrobial product to an HVAC&R system represents a use pattern substantially different from other hard surface disinfection or sanitizer treatments. Application to HVAC&R systems may require that larger volumes of the antimicrobial be applied to both internal and external system components than would typically be used as a disinfection/sanitizer application to a hard surface such as a desktop. Thus, there is a greater potential for the applicator to be exposed to large amounts of pesticide. In addition, many of the components of HVAC&R systems are typically inaccessible and could create unique exposure scenarios for applicators. Post-application exposure to building occupants is also a concern. When the treated system resumes operation, the potential exists for the pesticide to be readily spread throughout the building.

For these reasons, the Agency is proposing to modify the requirement for 90–day subchronic studies to address HVAC&R uses. Specifically, the Agency is proposing to replace the 90–day oral toxicity test with two 90–day toxicity tests, one by the dermal route, and one by the inhalation route. These are the primary routes of exposure from HVAC&R uses, and such route-specific studies are intended to provide the Agency with the information needed to characterize the hazard for the risk assessment for HVAC&R uses of antimicrobial pesticides.

I. Chronic Studies

Currently in part 161 a chronic toxicity study in two species is required for all food-uses and conditionally required for all other use patterns. Today the Agency is proposing to continue this existing requirement by requiring a chronic study in the rodent for high human exposures and conditionally requiring the study for low human exposures.

In its final rule for conventional pesticide chemicals, the Agency eliminated the requirement for an oral chronic study in a second, non-rodent species, usually the dog. Similarly, EPA is proposing to eliminate the 1–year dog study as a data requirement for antimicrobial pesticides. EPA's reasoning is fully explained in the final rule (Unit X) for conventional pesticides (Refs. 36, 37, and 38). For antimicrobials EPA would adopt the same criteria (as set out in the applicable test note to the table in proposed § 158.2230) for the rare circumstances when a 1–year dog study might be required.

J. Carcinogenicity Studies

Currently in part 161 two carcinogenicity studies are required for all food-uses and conditionally required for all other use patterns. Today the Agency is proposing to continue this existing requirement by requiring carcinogenicity studies in two species for high human exposures and conditionally requiring the studies for low human exposures.

K. Prenatal Developmental Toxicity

The Agency proposes to require two oral prenatal developmental toxicity studies (one in rodents and one in a non-rodent species) to support the registration of every antimicrobial pesticide product. This not only codifies the Agency's current practices, but also harmonizes the requirements for antimicrobials with those of conventional pesticides.

The Agency encourages applicants for registration to consider the use of combined study protocols in satisfying this requirement. A prenatal developmental toxicity study segment could be added to a two-generation reproduction study in rodents. By combining protocols, a single study could satisfy the requirement for both prenatal developmental and reproductive toxicity in the rodent. While it is recognized that the cost of the reproduction study would increase somewhat due to the additional work scope, the total cost of the combined study would be substantially less than that incurred by conducting the two studies separately. Moreover, a combined reproduction/developmental protocol should not require the use of additional animals and would increase the efficient utilization of the animals being studied. The second required prenatal developmental toxicity study in the non-rodent would then be performed separately.

The Agency may require an additional prenatal developmental study by another route of exposure (usually dermal) if there is evidence of developmental toxicity in any of the available studies and the other route of exposure is, in the Agency's judgment, a significant route of exposure (Refs. 3, 18, and 35). Submission of such a study is an infrequent occurrence: only one dermal prenatal developmental toxicity study has been submitted for an antimicrobial.

L. Reproduction

The Agency proposes to require a reproductive toxicity study to support the registration of every antimicrobial pesticide product. This codifies the Agency's current practices.

For many years, for nonfood-uses, the Agency did not require a reproductive toxicity study for low human exposure antimicrobials. However, in 1997, it was suggested that, without a reproductive toxicity study, the Agency could be missing reproductive risks of concern. For example, the Pest Management Regulatory Agency (PMRA) of Canada, presented the results of a retrospective analysis during the public comment portion of the FIFRA SAP in June 1997 (Ref. 13). Although the SAP did not comment on this analysis, the Agency determined that a reproductive toxicity study would ensure that it did not miss potential reproductive risks of concern.

In making the safety finding under FFDCA, the Agency is required to consider the special susceptibility/sensitivity of infants and children to pesticide chemical residues. EPA cannot adequately characterize the susceptibility of infants and children without a reproduction and fertility effects study that assesses the occurrence of biologically adverse effects on the male and female reproductive system, as well as on the developing organisms from exposure prior to conception (either parent), during prenatal development, or post-natally in the offspring up to the time of sexual maturation. Thus, to make the safety finding requires reproduction testing, since reproductive toxicity testing endpoints are not adequately assessed in the other required toxicity studies. Therefore, these other studies do not provide adequate ''triggers'' which would indicate the potential for reproductive toxicity.

Today's proposal harmonizes the requirements for antimicrobials with those of conventional pesticides. EPA has been requiring a reproductive toxicity study for all antimicrobials for the last several years.

As noted in Unit VIII.K. of this preamble, the prenatal developmental and reproductive toxicity testing requirements may be combined in a single study. If the applicant does not choose this option, then separate developmental and reproductive toxicity studies must be conducted.

M. Developmental Neurotoxicity (DNT)

In practice, EPA evaluates each pesticide using all available toxicological information that might indicate a need for a developmental neurotoxicity study. The DNT study has been required on a case-by-case basis for certain conventional chemicals for food-use and nonfood-use registrations since 1991.

Just as with conventional pesticide chemicals, the Agency is now proposing that DNT testing be conditionally required for all antimicrobial pesticides. This would be a new requirement for antimicrobial pesticides. The study is triggered based upon a weight-of-evidence evaluation of the toxicological database. The criteria involved in this weight-of-evidence evaluation are the same as those for conventional pesticide chemicals and are presented below:

1. The antimicrobial pesticide causes treatment-related neurological effects in adult animal studies, such as:
- Clinical signs of neurotoxicity.
- Neuropathology.
- Functional or behavioral effects.

2. The antimicrobial pesticide causes treatment-related neurological effects in developing animals, following pre- or post-natal exposure such as:
- Nervous system malformations or neuropathy.
- Brain weight changes in offspring.
- Functional or behavioral changes in the offspring.

3. The antimicrobial pesticide elicits a causative association between exposures and adverse neurological effects in human epidemiological studies.

4. The antimicrobial pesticide evokes a mechanism that is associated with adverse effects on the development of the nervous system, such as:
- SAR relationship to known neurotoxicants.
- Altered neuroreceptor or neurotransmitter responses.

EPA proposes the addition of the developmental neurotoxicity study to the toxicology testing requirements as a conditional requirement. The two required developmental toxicity studies do not include an in-depth assessment of the development of the nervous system and therefore do not provide the same information as the DNT. In implementing this conditional requirement, applicants are encouraged to apply what is known about the chemical and its toxicity to develop a rational, science-based approach to this testing.

N. Mutagenicity

Mutagenicity testing is required in part 161; however, just as with conventional pesticide chemicals, the Agency is proposing to change the specific types of tests to be performed to satisfy the mutagenicity testing requirement (Refs. 4 and 26). A battery of mutagenicity tests is currently required in part 161 to assess the potential of the test chemical to adversely affect the genetic material in the cell and subsequently serve as part of the Agency's weight-of-evidence approach for classifying potential human carcinogens. Mutagenicity data are also used to evaluate potential heritable effects in humans. Mutagenicity testing would no longer be subdivided into the categories of gene mutation, structural chromosomal aberrations, and other genotoxic effects, with selection from a wide range of mutagenicity tests satisfying these categories.

For conventional pesticides, the Agency requires in § 158.500 an initial battery for mutagenicity testing that consists of a bacterial reverse mutation assay with *Salmonella typhimurium* and *Escherichia coli*, an assay with mammalian cells in culture, and an *in vivo* cytogenetics assay. The Agency has selected the bacterial assay because it is a primary test for detecting intrinsic mutagenicity of many classes of biologically active chemicals. The genetics of each test strain of *Salmonella* and select strains of *E. coli* have been well-validated, and the assay is easy to perform, is used routinely throughout the world, and has an extensive data base of tested chemicals. The mammalian cells in culture assay will detect a wider spectrum of possible genetic endpoints not assayed in the bacterial test. The *in vivo* cytogenetics assay provides an important examination of the potential effect a test compound may have on an intact mammalian system. Data from this study provide information on *in vivo* metabolism, repair capabilities, pharmacokinetic factors (e.g., biological half-life, absorption, distribution, excretion) and target organ/tissue effects.

EPA is proposing to modify the requirement for a bacterial reverse mutation assay conducted with *Salmonella typhimurium* and *Escherichia coli.* For antimicrobials, it is not always practical to test antimicrobials for mutagenicity in bacterial test systems such as the bacterial reverse mutation assay. Most antimicrobial pesticides are toxic to bacteria, and therefore can only be tested at very low doses in bacterial assays. This means that, for antimicrobials, negative results in studies done in bacterial test systems do not necessarily demonstrate non-mutagenicity. Given this limitation of bacterial reverse mutation assays such as the Ames test, EPA must carefully review Ames studies conducted using antimicrobials. Cytotoxicity and the test levels used in the study are critical factors to consider when determining if the results of an Ames test is acceptable or not, that is, whether the test fulfills the data requirement. However, the Agency has previously accepted Ames tests for antimicrobials after review and evaluation indicates the validity of the results. If the results of the Ames tests are not valid, then the applicant would need to discuss other mutagenicity testing with the Agency, such as a forward mutation assay conducted using mouse lymphoma L5178Y cells. The test notes to the proposed mutagenicity requirements have been modified accordingly.

Since there are many different mutagenicity tests available besides those in the initial battery, other types of testing may have been performed in the course of product research and development. In addition to the initial battery, data from such mutagenicity tests must be submitted to the Agency, along with a reference list of all studies and papers known to the applicant concerning the mutagenicity of the test chemical. Having this information at the beginning of a mutagenicity assessment will greatly facilitate EPA's effort to provide a more accurate assessment of the mutagenicity of the antimicrobial pesticide in question.

O. Immunotoxicity

Just as with conventional pesticide chemicals, the Agency proposes to require immunotoxicity testing for all antimicrobial pesticides. This would be a new data requirement. Immunotoxicity testing is necessary to evaluate the potential of a chemical to produce adverse effects on the immune system. Immune system suppression has been associated with increased incidences of infections and neoplasia (abnormal and uncontrolled cell growth). In 1993, the National Research Council reviewed the technical literature and found that some pesticides are immunosuppressive (Ref. 19).

Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic function are inadequate to characterize a pesticide's potential immunotoxicity, even if some tissues subject to immunotoxic insult are examined. While data from hematology, lymphoid organ weights, and histopathology of routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict effects on immunotoxic function (Refs. 15 and 16). Therefore, the Agency is proposing to require functional immunotoxicity testing along with the data from immunotoxicity endpoints in other studies to predict the potential risk of pesticides on the immune system more accurately.

P. Metabolism and Pharmacokinetics

Currently in part 161 a metabolism study is required for all food-uses and conditionally required for all other use patterns. Today the Agency is proposing to continue this existing requirement by requiring a metabolism and pharmacokinetics study for high human exposures and conditionally requiring the study for low human exposures.

Q. Companion Animal Safety

Currently in part 161 a domestic animal safety study is conditionally required. According to the test note in § 161.340 this study would be required on a case-by-case basis. Today the Agency is proposing to continue this existing requirement by conditionally requiring the study for all antimicrobial use patterns. The test note specifies that the study would be triggered if the product's use would result in exposure to domestic animals.

R. Dermal Penetration

Currently in part 161 a dermal penetration study is conditionally required for all antimicrobial use patterns. Today the Agency is proposing to continue this existing requirement by conditionally requiring a dermal penetration study for all antimicrobial use patterns.

IX. Handler and Post-Application Exposure Data Requirements

A. General

Exposure data are used in the evaluation of the exposures to persons in occupational and non-occupational settings (§ 158.2260 and § 158.2270). For antimicrobials this includes residential, commercial and industrial, institutional, agricultural premises, and recreational sites. Data include dermal, inhalation, and non-dietary oral exposures.

Most past exposure research with antimicrobial products has studied either handler exposure (i.e., exposure of people who mix, load, or apply antimicrobial pesticides in the course of the application process or through other work-related tasks) or post-application exposure of people to residues of antimicrobial pesticides after application, in treated areas or on treated surfaces.

Handler exposure research may measure exposure to undiluted antimicrobial products as the products are mixed for application, or it may measure exposure to antimicrobial products diluted for use. Antimicrobial pesticide applicators may be industrial or other workers, professional applicators, or consumers using the product in or around their homes.

EPA considers handler exposure data essential for fulfilling its mandate to protect human health from pesticide risk, including aggregate and cumulative risk, and is therefore proposing to require handler exposure studies for all antimicrobial products, when the toxicity and exposure criteria are

triggered. Codifying this requirement would assist applicants for registration of antimicrobial pesticides to determine which studies are required and then to design and conduct acceptable studies measuring handler exposure.

Post-application exposure research measures exposures of people to residues of antimicrobial pesticides after their use or application, and thus does not involve the direct exposure that occurs during use. Of particular concern to EPA is the potential exposure of infants and children to post-application residues of products used in and around homes, daycare centers, or schools.

The data requirements proposed here are based on the Agency's current practice of requiring exposure data when certain toxicity and exposure criteria are met. These criteria are described in proposed § 158.2260 and § 158.2270. Today's proposal seeks to harmonize the exposure requirements for antimicrobials with those of conventional pesticides. The applicator (handler) exposure data requirements are the same as those codified for conventional pesticides. The post-application data requirements are the same as conventionals, with the exception of one study (Dislodgeable Foliar Residue and Turf Transferable Residues) that is not needed for antimicrobials.

The proposed requirement of such data for antimicrobial products when the toxicity and exposure criteria are triggered would allow the Agency to conduct more thorough exposure assessments for residential as well as occupational sites, and to cover all use and exposure scenarios for such sites. EPA presented the need for additional handler exposure data to the SAP in January 2007 (Ref. 39) and to the Human Studies Review Board (HSRB) in April 2007 (Ref. 40). Both groups agreed that additional data are warranted.

Research undertaken to address the proposed handler and post-application data requirements may involve intentional exposure of human subjects as those terms are defined in EPA's rules at 40 CFR 26.1102, and if they do, protocols and supporting documentation as specified in that rule must be submitted for review by EPA and the HSRB before any subjects are enrolled in the research. If research involving intentional exposure of human subjects is initiated without EPA's prior review, the resulting data will not be accepted in support of registration. Parties who are unsure whether proposed research involves intentional exposure are encouraged to consult with EPA before proceeding with the research.

B. Use of Surrogate Data

To support registration of an antimicrobial pesticide product, according to the proposed tables in § 158.2260 and § 158.2270, applicants would generate needed exposure data with a typical end-use product. However, the Agency recognizes the need to minimize the economic burden of generating data to meet human exposure data requirements while obtaining sufficient data and information for exposure and risk assessments. Whenever appropriate, surrogate data may be used for the assessment of antimicrobial pesticides. The Agency is currently working with several industry Task Forces that are generating exposure monitoring data that may be able to be used as surrogate data sources. The Antimicrobial Exposure Assessment Task Force (AEATF-II) is developing handler exposure data for antimicrobial applications (such as mopping, wiping, aerosol sprays, painting, etc.). Task Force members can consider using this surrogate data, if determined by the Agency to be suitable, to assess antimicrobial handler risk instead of generating their own data. If surrogate data are inadequate for the Agency to adequately predict likely exposures and the resultant risks, then applicants would need to submit chemical-specific and/or product-specific data.

C. Handler Exposure

The Agency proposes to require data addressing handler exposure for antimicrobials when the toxicity and exposure criteria are triggered. As discussed in Unit IX.A., this not only codifies the Agency's current practices, but also harmonizes the requirements for antimicrobials with those of conventional pesticides. EPA now proposes to codify these requirements in proposed § 158.2260 and set out explicitly in § 158.2260(b) the triggers describing the circumstances under which such data must be submitted.

For handler exposure, the proposed data requirements are as follows:

1. *Dermal exposure studies*. EPA proposes to require data for both outdoor and indoor dermal exposures to estimate the dermal exposure to persons directly handling pesticides. The number of exposure studies that may be required depends on the variety of use sites, their similarities, and whether the uses are indoor or outdoor. In the absence of surrogate data, generally, the selection of the appropriate testing site(s) is based on the exposure sites with the highest potential for exposure. Generally, this is determined based on the label uses and use rates. Consultation with the Agency is recommended for determining the appropriate use site(s) for testing. Studies of dermal exposure are often designed to concurrently measure inhalation exposure.

2. *Inhalation exposure studies*. Just as with the dermal exposure studies, EPA proposes to require data for both outdoor and indoor inhalation exposure studies. In the absence of surrogate data, generally, the selection of the appropriate testing site(s) is based on the exposure sites with the highest potential for exposure. For inhalation exposure studies, the use sites with the potential for the highest exposure are almost always indoors. Based on its experience, the Agency believes potential exposure is highest indoors because the pesticide is confined in a closed area and therefore is less likely to be rapidly diffused or dispersed. This means that if the application rates are the same for an indoor scenario and an outdoor scenario, then the Agency may require only the indoor inhalation study, as that would have the highest potential exposure. Consultation with the Agency is recommended for determining the appropriate use site(s) for testing. Studies of inhalation exposure are often designed to concurrently measure dermal exposure.

3. *Biological monitoring*. Biological monitoring is the only type of applicator exposure study proposed as a conditional requirement. Data from biological monitoring studies provide the Agency with estimates of the internal dose or amount of a pesticide in the body. EPA proposes to allow the submission of biological monitoring data in addition to, or in lieu of, dermal or inhalation exposure data, provided the human pharmacokinetics of the pesticide residue is sufficiently understood to permit the back calculation to determine the total internal dose, and providing further that there are adequate analytical methods available. Biological monitoring offers the advantage of assessing the internal dose, as opposed to the exposure or amount of chemical coming in contact with the surface of the skin or available for inhalation in the lungs as measured using passive dosimetry techniques. Because biological monitoring is necessarily specific to the material tested, generally it cannot be conducted using a surrogate chemical.

4. *Data reporting and calculations*. EPA proposes to require applicants to submit data reporting and calculation information whenever applicator exposure data are submitted. These data are needed by Agency scientists for an

appropriate level of review and evaluation, and offer a submission format that the Agency has found useful. This information is important because it allows EPA to assess the quality and validity of the exposure study and thus the accuracy of the estimates and resultant exposure calculations derived from that study. The types of information that would be included under this data requirement include:

- The chemical formulas used in the calculations.
- The data used in the calculations, including the raw data manipulation/correction used in order to calculate limits of detection/limits of quantification.
- The statistical analyses required.
- The quality control data for lab/field recovery and storage stability.
- The actual calculations.

Included within the data reporting and calculations requirement would be information on the ethical conduct of the research. EPA regulations at 40 CFR 26.1303 require that the ethical conduct of all research involving human subjects be fully documented at the time of submission of the data resulting from the research. This requirement will apply to all exposure studies involving human subjects submitted to EPA under the pesticide laws, without regard to whether the research involves intentional exposure. Data from exposure studies not accompanied by the required documentation of ethical conduct will not be accepted for review.

5. *Product use information*. EPA is proposing to require product use information for both occupational and residential use patterns. Product use information assists EPA to more accurately assess pesticide exposure to applicators by describing how the pesticide is actually used and applied. EPA requires this information because differences in use can translate to significant differences in exposure, and thus in risk. For applicator exposure, use information may include, but is not limited to, who applies the antimicrobial pesticide, the use sites, site locations, use directions, application rates and frequencies, application equipment and methods, protective equipment used, protective clothing worn, and other information that will determine exposure to antimicrobial pesticide handlers.

The Agency acknowledges that the guideline for applicator product use information has not yet been finalized. However, the guideline for applicator product use information should be substantially similar to the one for post-application. The guideline for post-application product use information was presented to the FIFRA Science Advisory Panel (SAP) in March 1998. (The draft guideline is available at *http://www.epa.gov/scipoly/sap/meetings/1998/march/contents.htm*.) The Agency will finalize both guidelines before publishing a final rule establishing antimicrobial data requirements.

D. Post-Application Exposure

The current data requirements for post-application exposure in § 161.390 are focused on reentry to treated areas by agricultural workers. Since the promulgation of these requirements in 1984, the Agency has become increasingly concerned about post-application risks to persons in occupational settings other than conventional food, feed, and fiber crop agriculture. The Agency is now proposing to require post-application exposure data for other settings where people may be exposed, regardless of whether they are on-the-job or bystanders. Under current practice, post-application exposure data are generally required for occupational and residential settings on a case-by-case basis when specific toxicity and exposure criteria have been met. Moreover, FFDCA mandates that EPA perform additional scientific analyses which before 1996 had not been a routine part of the Agency's risk assessment process, including the assessment of aggregate exposures from multiple pathways including dietary and non-dietary routes of exposure.

The Agency proposes to require data addressing post-application exposure for antimicrobials when the toxicity and exposure criteria are triggered. Two new exposure data requirements (soil residue dissipation and non-dietary ingestion exposure) are today proposed for antimicrobials. As discussed in Unit IX.A., this not only codifies the Agency's current practices, but also harmonizes the requirements for antimicrobials with those of conventional pesticides. EPA now proposes to codify these requirements in proposed § 158.2270 and set out explicitly in § 158.2270(b) the triggers describing the circumstances under which such data must be submitted.

For post-application exposure, the proposed data requirements are as follows:

1. *Soil residue dissipation*. These data are needed to characterize exposures to residues of antimicrobials, and most particularly wood preservatives, that occur through contact with outdoor soils. This information is critical for assessing risks to children who play around and are in contact with treated wood structures such as decks, play sets, and gazebos, and the surrounding soils. This would be a new data requirement for antimicrobials. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

2. *Indoor surface residue dissipation*. The Agency proposes to require the indoor surface residue dissipation study (sometimes known as a surface wipe sampling study). This study supplies information on residue dissipation from treated areas and articles such as carpets, hardwood floors, and counter tops, after antimicrobial pesticides have been used. It is also used to determine residue dissipation from decks and other structures manufactured from treated wood.

These data would quantify residue loads and characterize the dissipation rate (i.e., how fast pesticide residues disperse over time following application) of antimicrobial pesticides on indoor surfaces. The Agency could then assess the magnitude and duration of human exposure to antimicrobials present as surface residues. Without such data, the Agency has no precise means of calculating human exposures to such substances from contacting surfaces over time. This requirement would not apply to uses that are not surface treatments, e.g., aquatic areas, swimming pools, antifoulant coatings and paints.

The draft guideline for indoor surface residue dissipation is available at *http://www.epa.gov/scipoly/sap/meetings/1998/march/contents.htm*. This draft guideline was externally peer-reviewed before presentation to the SAP in 1998. An examination of the FIFRA SAP website since 1998 to the present will show many presentations to the SAP on assessing occupational and residential exposures. Science has evolved in this area.

EPA notes that it has reviewed and accepted many studies, on a case-by-case basis, that were not conducted in accordance with current guidelines, but which serve its needs and provide suitable information for risk assessment purposes. The guidelines themselves do not impose mandatory requirements. Instead, they present recognized standards for conducting acceptable tests, guidance on evaluating and reporting data, definition of terms, and suggested study protocols. The draft guideline, therefore, serves as a starting point for pre-protocol submission meetings where the Agency's scientists can provide guidance to registrants or task forces on aspects of study design.

The Agency's scientists are always willing to work with individual registrants to develop study designs to fulfill data requirements. The Agency will finalize this guideline before publishing a final rule establishing antimicrobial data requirements.

For wood preservatives, EPA has worked with the Consumer Product Safety Commission (CPSC) to develop methodologies for conducting surface wipe sampling studies on wood. Protocols for wood preservative treated surface wipe sampling studies must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

3. *Dermal exposure*. EPA proposes to require dermal exposure data for both outdoor and indoor dermal exposures to estimate the dermal exposure to persons exposed after the pesticide application has been completed. The discussion in Unit IX.C. of this preamble for handler dermal studies is also applicable to post-application exposures.

4. *Inhalation exposure*. EPA proposes to require inhalation exposure data for both outdoor and indoor inhalation exposures to estimate the inhalation exposure to persons exposed after the pesticide application has been completed. The discussion in Unit IX.C. of this preamble for handler inhalation studies is also applicable to post-application exposures.

5. *Biological monitoring*. A conditional requirement for biological monitoring data was discussed in Unit IX.C. That discussion is also applicable to the proposed conditional requirement for biological monitoring for post-application exposure which codifies the Agency's current practices.

6. *Product use information*. EPA proposes to require product use information for all antimicrobials. Such information has been routinely submitted to EPA by applicants and is now being codified as a separate and distinct requirement. For post-application exposure, required product use information includes information on reapplication rates and frequencies, post-application entry restrictions, re-entry intervals, rinsing and other residue removal practices, and other use data relevant to exposure after application. The draft guideline for post-application product use information is available at *http://www.epa.gov/scipoly/sap/meetings/1998/march/contents.htm*. The Agency will finalize this guideline before promulgating a final rule establishing antimicrobial data requirements.

7. *Description of human activity*. For post-application exposure the Agency is proposing to require a description of human activities. Information on those persons who may enter treated areas after the application is complete has been routinely submitted to EPA by applicants and is now being codified as a separate and distinct requirement

These data will allow for a more accurate evaluation of the exposure potential associated with use of an antimicrobial pesticide. The description of human activity data would define the activity patterns that affect exposures (e.g., defining the exposed populations in commercial/institutional and residential settings, the application sites, site-specific information on exposure time per activity, type of protective clothing worn, and any other relevant use activity data). The description of human activity information would be used with the use information (both application and post-application), to help the Agency determine whether the exposure potential for humans is likely to be significant, and if additional data will be needed.

8. *Data reporting and calculations*. EPA proposes to require applicants to submit data reporting and calculation information whenever post-application exposure data are submitted. Such information has been routinely submitted to EPA by applicants as part of any submission of exposure data and is now being codified as a separate and distinct requirement. The discussion in Unit IX.C. of this preamble for handler data reporting and calculations is also applicable to post-application exposures. Note in particular the discussion of the requirement at 40 CFR 26.1303 for full documentation of the ethical conduct of all submitted research involving human subjects, whether or not they were intentionally exposed.

9. *Non-dietary ingestion exposure*. The Agency proposes to require a non-dietary ingestion exposure study for residential types of exposures only. This study is not required for occupational exposures since the primary concern for adult workers is exposure via the dermal and inhalation routes. This would be a new data requirement that evaluates the potential oral exposures to humans, particularly children, from antimicrobial pesticide residues from sources other than food.

Note that EPA regulations at 40 CFR 26.1203 prohibits, without exception, conduct of any research intended for submission to EPA under the pesticide laws which involves intentional exposure of children under 18. Thus, any study of potential exposure of children, oral or by any other pathway, to antimicrobial pesticide residues must only be an observational study, involving no intentional exposure of children.

Incidental oral exposure via hand-to-mouth, object-to-mouth and direct mouthing/ingestion is an important exposure pathway for infants and toddlers. The results from these studies will be used to assess the risks associated with the incidental ingestion of antimicrobial pesticides by children following antimicrobial pesticide applications in residential or public settings, or exposure to treated surfaces (e.g., carpets, toys, wood structures). This study would be required for uses in and around the home, daycare centers and schools.

The Agency is primarily concerned with non-dietary exposures immediately following application of the antimicrobial pesticide; therefore, dissipation studies alone would not provide the information needed to assess risks from non-dietary ingestion. Information such as frequency/duration of hand-to-mouth activities and surface area mouthed are often needed as input values for the calculations that are performed to assess non-dietary ingestion exposure. When appropriate, EPA's Exposure Factors Handbooks (see *http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20563*) can be used as the source of this frequency/duration information. However, the data in these Handbooks cannot replace chemical-specific information from studies of treated articles/surfaces that quantifies the amount of pesticide residue on such surfaces.

Non-dietary ingestion may also occur through hand-to-mouth or object-to-mouth transfer of antimicrobial pesticide residues during activities performed by children (e.g., crawling) that put them in close proximity with treated surfaces. Non-dietary ingestion exposure would be expected in residential or public (e.g., schools, daycare) settings following exposures to:

- Soils in contact with, or adjacent to, preservative-treated wood structures such as play structures.
- Outdoor surfaces such as decks.
- Indoor surfaces such as antimicrobial pesticide-treated paint chips, or antimicrobial-sprayed floors or walls.
- Antimicrobial-treated textiles, polymers, or other items (e.g., clothing, bedding, carpets, or toys).

Non-dietary ingestion studies would, for example, monitor the amounts of pesticide residues in the rinsate from hand washing, and thus allow the Agency to develop science-based models or formulas to estimate

inadvertent exposure. The draft guideline for non-dietary ingestion is available at *http://www.epa.gov/scipoly/sap/meetings/1998/march/contents.htm*. This draft guideline was externally peer-reviewed before presentation to the SAP in 1998. An examination of the FIFRA SAP website since 1998 to the present will show many presentations to the SAP on assessing occupational and residential exposures. Science has evolved in this area.

EPA notes that it has reviewed and accepted many studies, on a case-by-case basis, that were not conducted in accordance with current guidelines, but which serve its needs and provide suitable information for risk assessment purposes. The guidelines themselves do not impose mandatory requirements. Instead, they present recognized standards for conducting acceptable tests, guidance on evaluating and reporting data, definition of terms, and suggested study protocols. The draft guideline, therefore, serves as a starting point for pre-protocol submission meetings where the Agency's scientists can provide guidance to registrants or task forces on aspects of study design. The Agency's scientists are always willing to work with individual registrants to develop study designs to fulfill data requirements. The Agency will finalize this guideline before publishing a final rule establishing antimicrobial data requirements.

X. Residue Chemistry Data Requirements

A. General

EPA proposes to adapt the basic residue chemistry data requirements (§ 158.2290) as listed in subpart O of current part 158 to support applications for antimicrobial products. However, EPA also proposes to modify the applicability of those requirements to reflect the differing risks and levels of exposure of antimicrobials. Residue chemistry data are used by the Agency to estimate dietary exposure to pesticide residues from food. If there are no direct or indirect food uses for the antimicrobial, then no residue chemistry data are required.

The proposed changes will allow EPA to better estimate human dietary exposure to antimicrobial residues in or on food or feed, to more accurately assess tolerances and tolerance exemptions, and to provide additional tools for the enforcement of pesticide residue tolerances to ensure that food entering the commercial market meets the ''reasonable certainty of no harm'' standard under FFDCA.

The residue chemistry database is designed to determine the composition of the pesticide residue and how much of that residue is present in food or animal feed. Residue chemistry studies include those which define:

- The nature of the residue, i.e., metabolism studies.
- The magnitude of the residue, i.e., those studies which measure how much of the residue of concern is present in food, feed, and water.

Food-use pesticides require both types of studies. Both plant and livestock metabolism studies are needed to determine the breakdown of the pesticide chemical in a living system, that is, whether the chemical stays intact or is converted into metabolites. Occasionally, the metabolites are toxic and are included in the analyses as a residue of concern. Magnitude of the residue (MOR) studies are performed to determine the level of residues of concern in food. Data collection residue analytical methods are reviewed by EPA as part of the validation of the metabolism and MOR studies which are used to establish tolerances.

In addition to dietary risk assessments, residue chemistry data are used to establish pesticide tolerances, the maximum level of pesticide residue that may remain on food. Because these are legal limits enforced by FDA, enforcement methods for detecting the presence and amount of the residue are needed, and are used by FDA, USDA, and the States for food inspection purposes.

There are distinct differences between the residue chemistry requirements of conventional pesticides that are applied to crops in a field setting and those of antimicrobials that are more likely to be applied in a confined setting such as a food processing plant. Those differences are reflected in the data requirements. For example, no migration studies are required for terrestrial food and feed uses in part 158, subpart O, and no rotational crop studies are required for any antimicrobial uses. Certain test notes in part 158, subpart O and in subpart W are also different. As expected, the differences result from the different use patterns.

Units X.B. and C. of this preamble discuss the two main categories of food-uses for the purpose of antimicrobial residue chemistry data requirements, direct and indirect. Units X.D. through Q. of this preamble explain changes to specific residue chemistry data requirements appropriate to antimicrobials. For the purpose of determining antimicrobial residue chemistry data requirements, most antimicrobial pesticides will be classified as either direct or indirect food uses, which are generally delineated in Units X.B. and C. of this preamble. For the purposes of defining the residue chemistry data requirements for antimicrobials, the table in proposed § 158.2290 further delineates direct and indirect uses into four categories: direct and indirect food uses, agricultural premises, and aquatic uses. Applicants should consult with the Agency on the appropriate category(ies) for their product.

B. Direct Food Uses

If the antimicrobial is applied directly to food or water, it is a direct food use. Such uses would include, but are not limited to:

- Livestock.
- Livestock feed.
- Drinking water for humans, livestock and/or poultry.
- Egg washes.
- Fruit and vegetable rinses.
- Aquatic areas that have the potential to contaminate potable water.
- Post-harvest applications that occur in the field, at a treatment facility (such as a packing shed), during transport, and while in storage, until the processing of the raw agricultural commodity begins.

No currently registered antimicrobial products are applied to agricultural field crops. Should an application for such an antimicrobial product be submitted to EPA, then the Agency would likely require the same data as specified in part 158, subpart O for other field-use pesticides applied to crops, as the test notes more accurately reflect the conditionalities of a terrestrial use pattern.

C. Indirect Food Uses

For the purpose of determining residue chemistry data requirements, an antimicrobial use is considered an indirect food use when the antimicrobial pesticide is applied to a surface or incorporated into a material that will subsequently contact food, that is, the pesticide is not applied directly to the food. Residues of the pesticide or its degradates can be transferred to the food when it comes into contact with these treated surfaces and articles.

Antimicrobial products labeled for treatment of hard non-porous surfaces which may come into contact with food (e.g., food area premises and equipment) are classified as indirect food contact uses. Sanitizers and disinfectants which remain on the surface of food-handling or processing equipment are indirect food uses. Sanitizers incorporated into articles (e.g., plastic products such as coffee cups or cutting boards) intended

for food contact are also indirect food uses.

Hard surfaces are considered to be food surfaces when food is prepared for consumption, either commercially or residentially on such surfaces. Examples of hard surfaces are eating utensils, dinnerware, pots and pans, cutting boards, food preparation surfaces, countertops, refrigerator shelves, refrigerator bins, ice trays, dining table tops, and cabinet shelves. Wood treated with an antimicrobial pesticide product could be used to construct or maintain a bee hive, a cattle trough or feeding station. These and other indirect contacts with food or feed are assessed to evaluate the need for a tolerance or tolerance exemption.

For the purpose of conducting a risk assessment for a sanitizer (an antimicrobial not rinsed from food-contact surfaces), the Agency uses the directions on the antimicrobial product label in combination with modeled data to determine the amount of the sanitizer remaining. Under this approach, EPA will initially assume that all of the sanitizer residues remain on the surface and thus have the potential to enter the food. This is a worst-case or screening-level assumption. EPA will then use this modeled estimate in combination with toxicity data to determine if there is a risk of concern and/or whether to establish a tolerance or tolerance exemption. If there are risk concerns and if scientifically appropriate, EPA may refine the estimate of residues remaining on the surface using more realistic model assumptions. If no risks of concern are identified using these refined assumptions, then most likely EPA would not require higher-tiered, measured surface residue data. Of course, as an alternative to the Agency's use of these screening-level or refined, modeled estimates, the applicant may provide data that measures the actual amount of sanitizer remaining on the treated surface or transferring to food.

For disinfectants (antimicrobials with potable water rinses) EPA proposes to generally follow the risk assessment approach outlined for sanitizer solutions. EPA would disregard the potable water rinsing and assume that worst-case residues (estimated using the sanitizer model) are available for entering food items. Alternatively, the applicant can provide data measuring the actual amount of disinfectant remaining on the surface or transferring to food after rinsing the treated surface.

If the antimicrobial is to be incorporated into products with food contact uses and bears a claim of surface sanitizing activity, the Agency will generally, in the absence of data, evaluate the need for a tolerance or tolerance exemption by assuming complete transference of the chemical into food over the lifetime of the treated product. Alternatively, the applicant may submit migration studies to demonstrate the rate or amount of transference of the antimicrobial into food items.

D. Chemical Identity

Currently in part 161, information on chemical identity is required for all use patterns. Today the Agency is proposing to continue this existing requirement by requiring information on chemical identity for all antimicrobial use patterns.

E. Directions for Use

Currently in part 161, directions for use are required for all use patterns. Today the Agency is proposing to continue this existing requirement by requiring this information for all antimicrobial use patterns.

F. Proposed Tolerance

Currently in part 161, a proposed tolerance is required for all food-use patterns. Today the Agency is proposing to continue this existing requirement by requiring a proposed tolerance for all antimicrobial food-use patterns.

G. Reasonable Grounds in Support of Petition

Currently in part 161, reasonable grounds in support of petition is required for all food-use patterns. Today the Agency is proposing to continue this existing requirement by requiring this information for all antimicrobial food-use patterns.

H. Submittal of Analytical Reference Standards

Currently in part 161, submittal of analytical reference standards is required for all food-use patterns. Today the Agency is proposing to continue this existing requirement by requiring submittal of these standards for all antimicrobial food-use patterns.

I. Nature of the Residue in Plants

The Agency proposes to continue to require a nature of the residue study in plants for aquatic uses and direct food contact uses. The Agency proposes to continue to conditionally require this study to support agricultural premise uses.

J. Nature of the Residue in Livestock

The Agency proposes to continue to require a nature of the residue in livestock study to support agricultural premise uses. The Agency is also proposing to continue to conditionally require a nature of the residue in livestock study to support direct food contact uses and aquatic areas. As with the data requirements for conventional pesticide chemicals EPA is proposing to change the chemical substance with which the test is performed. This would codify existing practices.

For antimicrobials used to treat animal drinking water, or to treat wood in contact with animals or animal feed, or in aquatic areas, the Agency proposes to change the test substance for the nature of the residue in livestock study from ''pure active ingredient, radiolabeled (PAIRA) and plant metabolites'' to ''PAIRA or radiolabeled plant metabolite.'' The test substance ''metabolites'' will be changed to ''metabolite'' to clarify that dosing with more than one compound in any one study is not acceptable. This is needed because in studies involving simultaneous dosing with both the active ingredient and plant metabolites, it is impossible to determine the amount of metabolite due to active metabolism from that introduced through intentional dosing. Simultaneous dosing with the active ingredient and any metabolites may not produce useful results, because the active ingredient and metabolites may have different metabolic pathways that cannot be differentiated. In most cases dosing with only the parent compound is necessary. However, in cases where plant and animal metabolites are found to differ, separate studies in which livestock are dosed separately with each unique plant metabolite may also be required.

The Agency proposes to specify in the test note that the livestock metabolism study would be required when an antimicrobial is applied directly to livestock, to livestock premises, to livestock drinking water, to livestock feed, or to crops used for livestock feed. This would also include antimicrobial uses to treat wood in contact with animals or animal feed, or in aquatic areas given the potential use for crop and livestock production. Such applications may result in both oral and dermal exposure of animals to the pesticide and, depending on the results, may necessitate magnitude of the residue studies to quantify the residues in meat, milk, poultry, and eggs.

K. Residue Analytical Methods

EPA proposes to require development and submission of analytical methods whenever a numerical tolerance is established. Residue analytical methods have two primary purposes:

- To collect residue data for establishing tolerance levels and

conducting dietary exposure assessments.

- To enforce the tolerances established by EPA in 40 CFR part 180.

Residue analytical methods are currently required in part 161, and EPA proposes to continue this requirement. These methods are required only if a numerical tolerance is established and since numerical tolerances are rarely established for antimicrobials, submission of this data should be a rare occurrence.

In part 158, subpart W, EPA is proposing to create separate entries in the proposed table in § 158.2290 for these two types of residue analytical methods to clearly indicate the need for both types of methods, or a method that can be used for both data collection and enforcement purposes. EPA believes that the separation of the combined requirement into separate and distinct requirements will provide clarity to applicants.

The enforcement method has the following characteristics:

- Analyzes for the residues of regulatory concern, i.e., those named in the established tolerance.
- Is reasonably rapid (typically one day or less).
- Uses readily available equipment and reagents.
- Must be clearly and completely described in a stepwise manner such that laboratory personnel competent using similar procedures can successfully perform the procedure on the first trial.
- Is subject to an independent laboratory validation.
- Has a mechanism to confirm the results.

The data collection method has the following characteristics:

- Analyzes for all residues of toxicological concern.
- No limitation on duration of procedure.
- May use specially-developed and very expensive equipment.
- Validation is subject only to internal laboratory controls.

If the applicant can develop one method and the Agency finds that this one method satisfies the criteria for both the enforcement and the data collection method, then only one method needs to be submitted. Otherwise, two methods must be submitted. For the proposed table in § 158.2290 the ''Rs'' and ''CRs'' specified in the residue analytical method data requirements reflect the Agency's best professional estimate of the likelihood of a numerical tolerance being established for an antimicrobial pesticide chemical and thus resulting in the requirement to submit the data.

As with the data requirements for conventional pesticide chemicals, the Agency proposes to change the chemical substance for residue analytical methods from ''TGAI and metabolites'' to ''residue of concern.'' This would codify existing test practices.

As with conventional pesticide chemicals (subpart O of part 158), the Agency is proposing to require an independent laboratory validation (ILV) of residue analytical methods to ensure the accuracy and reproducibility of data used for tolerance enforcement purposes. Codifying this current (since 1988) practice (Ref. 28) would promote development of clearly written, complete descriptions of analytical methods that can be used by Federal and State enforcement agencies.

L. Multiresidue Method Testing

The current requirement in 40 CFR part 161 for residue analytical methods actually encompasses several submissions to the Agency. The first is the chemical-specific method(s) discussed in Unit X.K. of this preamble and the second is the multiresidue testing. In promulgating its part 158 conventional pesticide data requirements, the Agency separated this combined requirement into separate and distinct requirements. EPA is proposing to do the same for antimicrobial pesticides.

Today, the Agency is proposing to codify the requirement for testing the residue of concern of the antimicrobial pesticide using the FDA's and the USDA's multiresidue methods (MRM) as a separate data requirement. As above, the Rs and CRs in the proposed table in § 158.2290 reflect the Agency's best professional estimate of the likelihood of a numerical tolerance being established. This testing is required only if a numerical tolerance is established and since numerical tolerances are rarely established for antimicrobials, submission of this data should be a rare occurrence.

MRMs are important components of pesticide monitoring and enforcement programs. In food monitoring programs, such as those of FDA and USDA, it is not practical or feasible to test for each individual pesticide in a separate test. The MRMs are used to detect the presence of many pesticides, and then if needed, re-testing is done with the chemical-specific tolerance enforcement method. Since the residue analytical method requirement is intended to refer to a method that is specific for one pesticide (sometimes called a ''single residue method'') and the multiresidue methods currently in use are designed to measure as many pesticides as possible, it is clearer to list these as two separate data requirements.

M. Storage Stability

As with conventional pesticides, the Agency proposes to add a storage stability study as an explicit requirement to validate the results of the various magnitude of the residue studies. Such data have been required previously as a part of the magnitude of the residue study, but will now, as with conventional pesticides, be codified as a separate requirement. As discussed in a test note to the proposed table in § 158.2290 storage stability data are required for any food or feed use requiring magnitude of the residue studies unless analytical samples are stored frozen for 30 days or less, and the active ingredient is not know to be volatile or labile. This test note would clarify when storage stability data are needed and also harmonizes the requirements for antimicrobials with those of conventional pesticides.

Magnitude of the residue studies address how levels of pesticide residues in samples of human foods and livestock feeds are determined. These samples are often stored for extended periods of time prior to analysis. Since tolerances are based on residues at the time of harvest (or sample collection) and the residues may be lost by processes such as degradation and volatilization during storage prior to analysis, storage stability data predicting the pattern of degradation, if any, of residues during this period are critical to understanding the results of the field trial studies.

N. Magnitude of Residue (MOR) Studies

As with conventional pesticides, the Agency proposes to change the test substance from EP (end-use product) to TEP (typical end-use product) for the following types of MOR studies: Crop field trials, processed food or feed, potable water, fish, irrigated crops, and food handling studies.

Residue data are needed for only one TEP of each formulation type used on a given commodity or site. When newer or other types of formulations are proposed for use, either additional residue data can be submitted to show that the use of these new or different formulations result in residues comparable to those arising from the original formulation for which residue chemistry data already exist, or side-by-side bridging studies can be conducted for the different types of formulations. If the new formulation results in residues higher than those from use of the original formulation, then the same number of trials would generally be

required for the new formulation as was required for the original formulation. This would codify a longstanding practice at EPA for various MOR studies. The Rs and CRs reflect the likelihood of the need for MOR studies in the Agency's best professional judgment. Test notes to the table in the proposed § 158.2290 describe the specific circumstances in which MOR studies may be required for an antimicrobial.

O. Magnitude of Residue in Meat, Milk, Poultry, and Eggs

Similar to the livestock metabolism study, the Agency proposes to change the test substance for the meat/milk/poultry/egg (M/M/P/E) MOR studies. Due to the difficulties in interpreting results of studies in which a mixture is fed, the Agency is currently discouraging the feeding of mixtures and is instead requesting the feeding of isolated compounds in livestock studies. Hence, to codify current practice, the test substance will be changed to read a single plant metabolite instead of metabolites in the plural. Provided that plant and animal metabolites are the same, the parent compound must be the test substance in livestock feeding studies. If any plant metabolite exists that is not also an animal metabolite, a separate feeding study may be required involving dosing with that unique plant metabolite. The Agency will inform the applicant when this additional testing is required. It is expected that this study will be rarely requested.

The Agency proposes to continue the conditional requirement for M/M/P/E MOR studies for agricultural premises, indirect food uses, direct food uses and aquatic uses. There are three types of M/M/P/E MOR studies: livestock feeding studies, direct livestock treatments, and agricultural premise treatments. The Agency proposes to clarify that livestock feeding studies generally are not required when (1) residues are not found in/on feed items or (2) livestock metabolism studies indicate minimal transfer of the pesticide residue to tissues, milk or eggs. For those pesticides which leave non-detectable or low residues in feed items and for which the livestock metabolism study shows little transfer of radioactivity to tissues, the Agency may be able to conclude that data on the level of residues in livestock and their byproducts are not necessary. Livestock premise treatment studies are required for those antimicrobials used to clean or otherwise treat livestock premises such as feedlots. These are expected to be the most common studies applicable to antimicrobials.

P. Anticipated Residues

The term ''anticipated residue'' (AR) refers to exposure data that would permit significant refinement of dietary exposure estimates. Refinement means that the Agency would estimate very realistic dietary exposure estimates after first using the screening-level estimates that allow EPA to perform a very quick, but conservative dietary risk assessment.

As previously discussed, no currently registered antimicrobial products are applied to agricultural field crops. Generally, for antimicrobial direct food-uses, when performing the initial, screening-level dietary risk assessment, EPA uses the antimicrobial tolerances as the input values for dietary modeling. If there are risk concerns and if scientifically appropriate, EPA may refine (that is to be more realistic) the input values by using data showing the pesticide residues in food closer to the point of consumption. Market basket surveys are an example of one source of residue data that could be used to generate more realistic dietary exposure estimates for direct food-uses. Anticipated residue data would be required when estimates of risk using residues at the tolerance level result in a risk of concern, and a more realistic estimate is needed.

However, antimicrobials also include indirect food uses such as sanitizers and disinfectants which remain on the surface of food-handling or processing equipment. For these indirect food-uses, generally when performing the initial, screening-level dietary risk assessment, EPA uses several high-end (over-estimated) assumptions as the input values for dietary modeling. In such an assessment, the same assumptions are used for every dietary assessment. Such an assessment can be performed quickly, and if there are no risk concerns, then the dietary assessment is considered to be complete. However, if there are risk concerns and as scientifically appropriate, EPA would begin a process of using the available information and data to refine, that is to be more realistic, in estimating input values.

Since the screening-level risk assessment did not consider the particular use pattern of the antimicrobial chemical, as a first refinement, EPA would modify the assumptions to account for the particular use pattern of the chemical. Refinements to the assumptions can also be made if measured data such as a migration study were available.

AR data would be required when estimates of risk have been refined using information and any measured data initially available to EPA, and these refined risks result in a risk of concern. Taking samples from treated hard surfaces is an example of one source of residue data that could be used to generate more realistic dietary exposure estimates for an indirect food-use.

If there is no food-use, then AR data would not be submitted to EPA. AR data would be a conditional requirement that is triggered only when estimates of risk conducted using residues at the tolerance level may result in a risk of concern. This means that AR data would be required only for a food-use, and only if a numerical tolerance is established, and then only if the risk assessment conducted at tolerance level results in a risk of concern. This would be an infrequent occurrence for antimicrobials. Establishing this data requirement for antimicrobials not only codifies the Agency's current practices, but also harmonizes the requirements for antimicrobials with those of conventional pesticides.

Q. Food Migration Studies

This study is unique to antimicrobials and this proposal codifies current practices. EPA is proposing to conditionally require a migration study for indirect food uses when modeled estimates of the amount of antimicrobial residues transferred to the food or feed may result in a risk of concern. This study would not be required for any other uses.

A migration study is performed to determine the amount of a chemical substance that can enter a food commodity through contact with a treated surface. There are two basic types of migration studies. The first type includes sanitizing and disinfecting solutions that are applied to equipment in a food-processing facility. The second type includes matrices such as wood, plastic, paper, cloth, or rubber which may be impregnated with antimicrobial pesticides. The migration of the antimicrobial into the food occurs when the food commodity comes into contact with the treated surface or the impregnated matrix.

As previously discussed, the Agency believes that it is possible to model a worst-case estimate of the amount of the antimicrobial chemical that migrates into the food commodity. If the worst-case estimates do not result in a risk of concern, then the applicant would not need to submit a migration study. As an alternative to these worst-case estimates, the applicant may provide data for the

amount of sanitizer/disinfectant remaining on the surface.

There is no Agency guideline for conducting a migration study. EPA routinely accepts studies performed according to FDA's food migration protocol/guidance. Applicants are encouraged to use existing FDA methodologies. Information that could be of value to applicants developing protocols is on the FDA website (Refs. 7, 9, 10, and 11). Protocols must be approved by the Agency prior to the initiation of the study. However, if a migration study has been reviewed and accepted by FDA, then this fact should be included in the submission to EPA, along with the migration study.

XI. Environmental Risk Assessment

A. General

Environmental fate studies evaluate the mobility, distribution and dissipation of a pesticide in various compartments of the environment, such as water, soil, air, and sediment. These studies are designed to identify which dissipation processes are likely to occur when the pesticide is released into the environment and characterize the significant degradates likely to result from these processes. Data from these studies are used as inputs in exposure models, and, in conjunction with ecological effects studies, are used to assess whether a pesticide has the potential to cause adverse effects to wildlife, fish, plants, and humans. Environmental fate studies are discussed in Unit XII. of this preamble.

Ecological effects data are used by the Agency to determine the toxicological hazards of pesticides to various nontarget organisms, such as birds, mammals, fish, bees, terrestrial and aquatic invertebrates, and plants. These tests include short-term acute, subacute, reproduction, simulated field, and full field studies arranged in a tiered system that progresses from the basic laboratory tests to the applied field tests. Ecological effects testing for nontarget organisms are discussed in Unit XIII, and nontarget plants in Unit XIV of this preamble.

These data provide a foundation for an environmental risk assessment. The results of the environmental fate assessment are evaluated in conjunction with the results of the ecological effects data to determine the potential of the pesticide to cause harmful effects to nontarget organisms and plants.

The Agency has divided the antimicrobial pesticides into two groups for determining environmental fate and ecotoxicity data requirements: the low environmental exposure grouping and high environmental exposure grouping as discussed in Unit XI.B.

B. Determination of the Two Groupings: Low and High Environmental Exposure

1. *Factors considered in determining the groupings.* As previously discussed, EPA is proposing to establish its 12 antimicrobial use patterns in § 158.2201. EPA examined these use patterns and identified those that occur outdoors, discharge effluent directly to the outdoors, or result in materials treated with antimicrobials (i.e., wood preservatives and antifoulants) being placed in the environment. Given this direct link to the environment, and correspondingly higher exposure potential, there is a greater potential for concern. In fact, EPA has been requiring more data for such use patterns than for other antimicrobial use patterns.

2. *The high environmental exposure grouping.* The Agency believes that the potential for environmental exposure is high for three of the use patterns and part of a fourth use pattern. For the purposes of requiring data, the following use patterns represent the high environmental exposure grouping for environmental fate (§ 158.2280) and ecotoxicity (§ 158.2240 and § 158.2250) data requirements:

- Once-through industrial processes and water systems (part of the industrial processes and water systems use pattern).
- Antifoulant paints and coatings.
- Wood preservatives.
- Aquatic areas.

The data that have been typically required for the use patterns now included in the high environmental exposure grouping are used to calculate estimated environmental concentrations (EECs) of the pesticide in different environmental media. These EECs are needed to conduct quantitative environmental and ecological risk assessments. These data would also have applicability to drinking water exposure assessments that are used in human health risk assessments.

3. *The low environmental exposure grouping.* The low environmental exposure grouping is defined as those use patterns that are not included in the high environmental exposure grouping. For the purposes of requiring data, the following use patterns represent the low environmental exposure grouping for environmental fate (§ 158.2280) and ecotoxicity (§ 158.2240 and § 158.2250) data requirements:

- Agricultural premises and equipment.
- Food-handling and 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.
- Swimming pools.
- Recirculating industrial processes and water systems (part of the industrial processes and water systems use pattern).

C. Data Requirements for Wood Preservatives

As discussed previously in this proposal, wood preservatives are considered to be an antimicrobial use pattern with high expectation of environmental exposure. Wood that has been treated with a wood preservative product is placed directly into the outdoor environment, thus leading to the potential for significant release of the wood preservative into the environment. The data required to register a wood preservative product depend on the use site of the treated wood, which can be land-only, aquatic-only or both. For instance, a wood preservative product which would be used in or near water will usually have more data requirements concerning the effects of the pesticide on aquatic organisms than a product that is not used in or near water.

Therefore, if a product specifies that wood that has been treated with that product cannot be used in areas with the potential for that wood coming into contact with water, then EPA believes that the potential for exposure is decreased. Accordingly, it is current EPA practice to require fewer environmental fate and ecological effects studies for such products. In practice it is difficult to assure that wood treated with a wood preservative that is for land-use only will not come in contact with water. Treated wood intended for a use with little potential aquatic exposure could be inadvertently diverted to other uses, such as marine docks or pilings, which would have considerable aquatic exposure. The Agency does not know if or how often this kind of diversion occurs. However, the Agency notes that in the United States, wood preservatives are categorized using the American Wood Preservers' Association Use Category system. These categories describe the exposure conditions which treated wood products can be subjected to when in service. The categories, although general, provide some measure of control over how treated wood products are used.

A concern that has been raised to EPA is the difference in how different countries regulate wood preservative products. This could present a challenge for joint reviews of wood preservatives since different data requirements and differing programmatic objectives could result in different regulatory decisions.

Today's proposed data requirements are based on EPA's current practice of determining the data required for a wood preservative product dependent on the usage (land-only versus land and aquatic). The Agency requests comments on the regulation of wood preservative products, and based on the comments received could continue with the split usage or determine to no longer have such a split usage.

XII. Environmental Fate Data Requirements

A. Environmental Fate Data Requirements for Antimicrobials

The Agency proposes to adapt the basic environmental fate data types (§ 158.2280) as listed in subpart N of current part 158 to support applications for antimicrobial products. EPA also proposes to modify the applicability of those requirements to antimicrobials to reflect differing risks and levels of exposure. Moreover, new types of data are needed to evaluate the risks associated with use patterns more typically associated with antimicrobials, such as discharge through sewer systems and wastewater treatment plants to the environment. As discussed in this Unit, such studies could include: Activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition test.

Fate studies characterize how a pesticide chemical dissipates once it is released into the environment, and identify the significant transformation products likely to result from these processes. Fate studies include both laboratory and field studies. Such studies can provide input parameters needed in simulation modeling. Under a tiered testing scheme, a specified set of laboratory studies determined by the use patterns is performed first, and then a preliminary, qualitative environmental fate and transport assessment is developed from the results of those lower-tiered studies and the modeling. This assessment could determine that no additional studies are needed. Or, this assessment could trigger higher-tiered laboratory-based studies, and/or to design or trigger appropriate field studies. Fate studies can also be used as triggers for determining which ecological effects data will be needed to support registration.

Once the higher-tiered studies have been reviewed and evaluated, then the Agency would use all these data to develop quantitative environmental fate and drinking water exposure assessments, and to calculate estimated environmental concentrations of the pesticide in different media (such as water, sediment, or soils) under various pesticide application and site scenarios. The Agency uses these estimates of exposure in conjunction with toxicity data to assess whether a pesticide has the potential to cause adverse effects on human health via exposure through drinking water and the environment via exposures through both water and soil.

B. History of Environmental Fate Data Requirements for Antimicrobials

In 1984, at the time of promulgation of the original part 158 data requirements, there were no environmental fate data requirements for the indoor use pattern. At that time, EPA assumed that many of the indoor uses went down-the-drain to a wastewater treatment plant (WWTP), at which point dilution and degradation, or removal by WWTP processes would mitigate environmental concerns. Thus, currently, in part 161, there are no environmental fate data requirements for the indoor use pattern.

In 1997, the Agency presented a draft of the antimicrobial data requirements to the FIFRA Science Advisory Panel (SAP) (Ref. 29). As part of its presentation EPA explained its intent to divide antimicrobial uses into two groupings based on the potential for environmental exposure (high environmental exposure and low environmental exposure). In 1997, the Agency defined the low environmental exposure grouping as the following eight use scenarios: Agricultural premises and equipment; 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; and swimming pools. For these eight use scenarios for environmental fate data the Agency intended to require a very reduced data set (hydrolysis data).

In its report, the SAP expressed its concerns about ''the lack of chemical fate data,'' indicated that hydrolysis would be an important pathway of concern for only a subset of antimicrobial chemicals, and stated that both biodegradation data, and microbial data should also be required. According to the SAP, this was ''to ensure the safety of environmental discharge but also for protection of publicly owned treatment works (POTWs) and other treatment systems which often rely on microbial treatment processes.'' In response to the SAP's concerns, the Agency reexamined the need for environmental fate data other than hydrolysis. As a result of this 1997 reexamination, the Agency determined to conditionally require data on photodegradation in water for low environmental exposures. At that time, the Agency determined not to require biodegradation or microbial data.

More recently, as part of its development of this proposed rule, EPA re-evaluated the 1997 SAP recommendations concerning the data requirements for environmental fate, and nontarget plant and organisms. The reason for this re-evaluation was, in part, due to certain comments that were received in response to the 2005 proposed rule for conventional pesticide chemicals (70 FR 12276, March 11, 2005). Additionally, the Agency was also becoming increasingly aware of detections of antimicrobial chemicals in various environmental compartments.

The Agency received comments from four California water treatment authorities and from environmental agencies from two cities in California. The comments centered on their strong recommendations that FIFRA data requirements should be equivalent to the data required to develop water quality criteria (WQC) under the Clean Water Act (CWA) and should consider water quality issues related to urban pesticide use. California water-treatment authorities questioned the adequacy of the Agency's assessment of risks with regard to water quality considerations including: Use of aquatic toxicity data, surface water quality studies, and urban uses of pesticides, particularly when these uses result in pesticide residues in receiving waters from storm sewers or sewage treatment plants.

EPA believes that even though these comments were received in response to the conventional pesticide chemicals proposed rule, the submitted information on receiving waters for wastewater treatment plants is particularly applicable to antimicrobials, many of which are used indoors. This means that the antimicrobial goes down-the-drain and eventually reaches a wastewater treatment plant. Therefore, in its response to comments document for the final rule for conventional pesticide chemicals, EPA agreed that pesticide discharge into municipal sewage systems is an important issue

particularly for those antimicrobial pesticides which are typically rinsed down the drain. EPA stated it would consider the issue of down-the-drain chemicals in the proposed rule for antimicrobials.

As a first step toward re-evaluating its processes and procedures for conducting a risk assessment for an antimicrobial chemical that goes down-the-drain, the Pesticide Program discussed these issues with EPA's Office of Water (OW). The Agency is becoming increasingly aware of detections of antimicrobial pesticide chemicals in various environmental compartments, including surface water. An example of a chemical with such detections is triclosan (Refs. 12, 17, 22, and 23). The detection of such chemicals in surface water indicates that the antimicrobial (or its degradate) is moving from the area of application, down-the-drain to a WWTP, and then into the environment via the treated effluent. Certain chemicals can pose a risk even at low levels. Based on the Agency's concerns about the potential effects of antimicrobials on the biological treatment processes used in WWTPs, concerns about potential bioconcentration of antimicrobials after release, and possible effects on nontarget species, the Agency now believes that new environmental fate data requirements are needed for down-the-drain antimicrobial uses.

Therefore, EPA is proposing to require data to address environmental fate (degradation), biodegradation data, and microbial data, for the low environmental exposure grouping (as defined in Unit XI.B. and once-through industrial processes and water systems. These data reflect the Agency's concern about the potential movement of antimicrobials and their degradates from the indoor environment to the outdoor environment. Additionally, these lower-tiered data will allow EPA to conduct screening-level environmental fate assessments which can then indicate the need for higher-tiered fate and ecotoxicity studies and higher-tiered environmental assessments.

EPA specifically requests comments on the Agency's rationale for requiring data to perform a screening assessment on down-the-drain antimicrobial uses, the potential for performing higher-tiered studies based on the results of the screening assessment, and the cost and burden of performing the studies.

EPA also notes that three use patterns, wood preservatives, antifoulants, and aquatic uses are not considered down-the-drain use patterns. As previously discussed, these uses either occur outdoors and thus discharge directly to the environment, or result in materials treated with antimicrobials being placed in the environment. Since these use patterns are unlikely to go down-the-drain, a screening-level environmental fate assessment is not needed.

C. Today's Proposal for Low Environmental Exposure Antimicrobials

The Agency believes that environmental exposures from the use patterns discussed in Unit XI.B.3. of this preamble are likely to be small, because (1) the sites where these uses occur are not rapidly or directly connected to aquatic environments, (2) some of the applications occur on a very infrequent basis and other applications involve very small amounts of the antimicrobial, and (3) in many cases wastewaters containing these antimicrobials are processed in WWTPs. The indirect movement of antimicrobials from the use sites into the outdoor environment occurs mostly through water. In many cases, leachates, rinsates, and flushes are released down-the-drain, and eventually reach a WWTP. WWTPs degrade chemicals in their influent, although the degree of degradation varies widely depending on the chemical, the treatment process and other factors (e.g., ambient temperature). After treatment, the effluent (the treated water and any chemicals remaining in that water) is released into the aquatic environment, or to the terrestrial environment via land application of sewage sludge.

Given the expectation of low exposures to the environment, EPA proposes to use a tiered system of data requirements to determine the type of environmental fate assessment needed for the low environmental exposure grouping. A screening-level assessment would be used to determine the potential of the antimicrobial chemical to directly harm the microbial treatment processes present in wastewater treatment systems, the environmental compartment(s) that the antimicrobial is likely to partition to, and the amount of antimicrobial that could be present in the effluent that the treatment plant releases to the environment. The presence of antimicrobials in an effluent release means that an ecological assessment could be required to evaluate risks to endangered species. It is also possible that estimation of concentrations to use in a drinking water assessment could be required.

The lower-tiered environmental fate studies being proposed for the screening-level assessment for the low environmental exposure grouping are discussed in detail in Units XII.E. – K. of this preamble. The higher-tiered studies that would be triggered are based on a weight-of-evidence evaluation of the results of the lower-tiered studies are discussed in Units XII.L. – Q. EPA's proposal to conditionally require these data for the low environmental exposure grouping would for these studies expand the number of use patterns for which the test is conditionally required.

It may be possible to model some of the needed parameters. The applicant is encouraged to review the approach discussed in Unit XVIII.A. of this preamble on the use of Structure-Activity-Relationship (SAR) assessments to ascertain if such techniques could provide useful information in preparing their submission to EPA.

EPA is proposing to conduct the screening-level of its fate assessment for these low environmental exposure antimicrobials with non-direct, delayed environmental connections in a three-pronged approach. The three prongs are designed to (1) estimate the number of days per year of exceedance of the antimicrobial surface water concentration of concern to aquatic organisms in a surface water body downstream of a treatment plant, (2) determine any negative effect of the antimicrobials in the influent on the activated sludge biomass in biological wastewater treatment systems, and (3) determine the potential for the antimicrobial to accumulate in sediment or in organisms downstream from the WWTP release, or for there to be negative impacts on nontarget organisms in the receiving water body.

For the first prong, modeling would be used to estimate a screening-level exposure concentration of the antimicrobial in a surface water body that receives effluent from a WWTP. EPA anticipates using the Down-the-Drain model with the Probabilistic Dilution Model (PDM) option in the Exposure and Fate Assessment Screening Tool (E-FAST) (Version 2.0) available from the Agency's website (see *http://www.epa.gov/oppt/exposure/pubs/efast.htm*). This model option uses readily available data as inputs to estimate conservative (i.e., high-end) exposure concentrations. E-FAST has been independently peer-reviewed by EPA's Science Advisory Board. Comments from that peer review have been incorporated into Version 2.0 of E-FAST.

The PDM option of E-FAST can predict downstream chemical concentrations from an industrial discharge and from disposal of consumer products into household wastewater. The module uses a simple

mass balance approach that uses probability distributions as inputs. The concentration of the chemical in the receiving surface water body is also calculated as a probability distribution of the ratio of WWTP effluent flow and stream flow immediately downstream of the WWTP. The Down-the-Drain Model can be run with or without the PDM option.

The Down-the-Drain Model requires as an input value the production volume of the chemical. If this information cannot be supplied by the applicant, then the Agency would need to estimate the volume. The production volume would be used as if the entire volume of the chemical were expected to go down the drain. However, the Agency would be able to modify the production volume to account for the percentage of the chemical that is expected to actually go down the drain. As an example, almost all of a toilet bowl cleaner can be reasonably expected to go down the drain, but a hard surface cleaner could also vaporize into the air, dry on the surface, or be disposed of on paper towels into the trash. Therefore it may be reasonable to adjust the production volume used as an input to the Down-the-Drain model. The model estimates human exposure from ingestion of drinking water and fish, and concentrations of chemicals in surface waters downstream of WWTPs. The PDM option estimates the number of days of exceedance of a concentration of concern for aquatic organisms. Concentrations of concern are based on measurements of acute and/or chronic effects to aquatic organisms.

For the second prong of the assessment, EPA intends to require five environmental fate studies to determine the potential of the antimicrobial to harm the microbial treatment processes in wastewater treatment systems, and to determine the potential amount of antimicrobial present in the effluent that the treatment plant releases to the environment. Higher-tiered studies would be triggered based on a weight-of-evidence evaluation of the results of the following lower tiered studies: Hydrolysis; photodegradation in water; modified activated sludge, respiration inhibition test; activated sludge sorption isotherm; and ready biodegradability. These tests are discussed in Units XII.E., F., H., I., and K. of this preamble.

- The data from the hydrolysis study would allow EPA to determine if the antimicrobial hydrolyzes in water during transport to the WWTP, and also after release to the environment. These data are routinely used to understand the persistence of a chemical in the environment, and when the hydrolysis breakdown products should also be considered in the environmental fate assessment.
- The data from the photodegradation in water study would allow EPA to determine if the antimicrobial degrades in shallow water due to exposure to sunlight. These data are used to understand the persistence of a chemical in surface water.
- The modified activated sludge, respiration inhibition test would allow EPA to identify antimicrobials which could harm the microorganisms found in biological wastewater treatment systems and would also indicate suitable antimicrobial concentrations for use in the ready biodegradability test.
- The activated sludge sorption isotherm study would allow EPA to assess the distribution of the antimicrobial between the sludge and aqueous phases.
- The ready biodegradability study would allow the Agency to determine whether the chemical tested achieves ''pass levels'' for ready biodegradability. These screening tests are so stringent that it is assumed that the chemicals that meet the pass levels will rapidly and completely biodegrade in aquatic environments under aerobic conditions.

Modeling could also be used to predict the removal of a chemical in a sewage treatment plant. STPWIN™ is part of the EPI SUITE modeling available via the Agency's website (see *http://www.epa.gov/oppt/exposure/pubs/episuite.htm*). STPWIN™ can predict values not only for the total removal but also three contributing processes: Biodegradation, sorption to sludge, and stripping to air.

The third prong of the fate assessment would use the available product chemistry data (for example octanol/water partition coefficient, vapor pressure, or solubility in water) or predicted/modeled data to determine the potential for the antimicrobial to bioconcentrate. This is consistent with the approach used in the Agency's PBT profiler, an assessment tool that estimates environmental persistence (P), bioconcentration potential (B), and aquatic toxicity (T) of a chemical based on its molecular structure. (see *http://www.epa.gov/oppt/pbtprofiler*.)

The Agency would then use the results of all three prongs to conduct a screening-level environmental fate assessment. It is also possible that information from open literature could be useful to the Agency for its assessment. By combining the modeled exposure estimates with information on the persistence of the antimicrobial, its distribution in the environment, and its ability to harm the microorganisms found in a biological WWTP, the Agency could determine if there are risk concerns. Based on the concerns, EPA would be able to determine if a more in-depth risk assessment would be required for certain environmental media. Higher-tiered data could be required to support such a risk assessment. The specific data would depend on the environmental medium in which the antimicrobial and its transformation products reside, and on the concentrations in the environment.

- If the antimicrobial is completely degraded to non-toxic degradates, then it is likely that no higher-tiered environmental fate data would be required.
- If the antimicrobial is not completely degraded by the WWTP and is in the effluent released to surface water, then depending on the concentrations that then occur in the environment, an assessment similar to that of an antimicrobial with high environmental exposure could be needed.
- If the antimicrobial partitions to water, then the possible higher-tiered environmental fate studies would include: Leaching and adsorption/desorption, and aerobic and anaerobic aquatic metabolism.
- If the antimicrobial is likely to partition to sludge, soil, or sediment, then possible higher-tiered environmental fate studies would include aerobic and anaerobic soil metabolism studies, and sediment studies. EPA has considered that antimicrobials may be present in biosolids (sewage sludge) that are land applied. While soil and sediment data would be required for an antimicrobial risk assessment, these data may also be useful to EPA's Biosolids Program conducted under 40 CFR part 503.

The Agency specifically seeks comment on this proposed approach for performing a screening-level environment fate assessment and the potential for triggering higher-tiered studies.

D. Case Studies

To assess whether the proposed approach provides the data needed to assess exposure and risk of antimicrobial pesticides released to the environment via down-the-drain use patterns, the Agency has conducted four case studies. All of the models used for the case studies are peer-reviewed, and publicly available. These case studies, entitled ''Four Case Studies of Antimicrobial Pesticides in the Down-the-Drain Screening Model, Using the Proposed Approach for a Screening-Level Environmental fate Assessment'' (Ref. 42) reflect a particular integration

of the modeling results specific to the needs of antimicrobials.

Four antimicrobial pesticides that have completed scientific review in the reregistration process were selected to represent a range of influent volumes to WWTPs, and general environmental fate and transport properties. Antimicrobials undergoing reregistration were chosen because they have fairly complete supporting data bases, and are well understood; that is, they allow a comparison of the proposed approach with real-world information.

In selecting these four chemicals, the Agency attempted to select at least one chemical that should trigger higher tier data requirements and one that should trigger no higher tier data requirements. The environmental fate and transport characteristics considered during the case studies were environmental persistence, biodegradability, hydrolytic stability, and sorption potential. Although not intended to represent all possible combinations of chemical characteristics, use scenarios, and usage volumes, the four antimicrobials selected for the case studies were intended to include a sufficiently broad range of possible outcomes to credibly assess the proposed approach.

- Chemical A was intended to represent a chemical with a high loading (mass) within the WWTP's influent, high toxicity to fish and aquatic invertebrates, high hydrolytic stability, relatively high potential to biodegrade during wastewater treatment, and low to moderate potential to adsorb to activated sludge. This chemical was picked as a ''worst-case'' example.
- Chemical B was intended to represent a chemical with a relatively low to moderate loading (mass) within the WWTP's influent, high toxicity to fish and aquatic invertebrates, high hydrolytic stability, and no available data on biodegradability during wastewater treatment or the potential to adsorb to activated sludge.
- Chemical C represents a ''best-case'' example. It is an organic acid that has a high loading (mass) within the WWTP's influent, potential to bioaccumulate, high water solubility, no environmental fate data, and no ecotoxicity data. This chemical was selected as a case study because it degrades quickly and would be expected to have little potential for ecotoxicity.
- Chemical D represents a mixture of two organic chemicals with relatively low loading (mass) within the WWTP's influent volume, high resistance to biodegradation during wastewater treatment, low potential to sorb to activated sludge, and fairly low toxicity to fish and aquatic invertebrates.

The specific identities of the antimicrobials have been ''blinded'' to focus those who may wish to comment on the proposed approach, and not what the result ''should'' be for a particular chemical.

Many, but not all, of the values selected for input data for the case studies were based on measured or estimated values for existing antimicrobial pesticides. In some instances, values for input data needed to run models to assess exposure and risk from down-the-drain releases were not available. In those instances, hypothetical values were used. Hypothetical values were also sometimes selected to enable the cases to have sufficiently different key environmental fate and transport properties to be able to more rigorously test the proposed tiered approach for assessing exposure and risk to chemicals that are released down-the-drain.

TABLE 1.—CASE STUDIES

Study	Results
Chemical A: A Chemical that Does Not Hydrolyze and Only Partially Biodegrades	The proposed approach indicated Chemical A has considerable potential to pose ecological concerns. Aerobic and anaerobic soil metabolism studies are needed to refine environmental fate and dissipation, and higher-tier ecotoxicity studies are needed to determine risk to nontarget species.
Chemical B: A Chemical Which Is Stable to Hydrolysis, But There Is No Data on the Potential to Biodegrade During Wastewater Treatment or Adsorb to Activated Sludge	The proposed approach indicated that the lower tiered environmental fate studies are needed to determine Chemical B's dissipation rate in wastewater treatment plants. Several higher tiered ecotoxicity studies are needed to determine risk to nontarget species.
Chemical C: An Organic Acid that is Highly Soluble in Water	There are no data to show that Chemical C would harm microorganisms found in biological wastewater treatment systems.
Chemical D: A Mixture of Chemicals	Chemical D does not appear to pose ecological risks at the assumed production levels. However, the potential for biodegradation and any potential impacts on waste water treatment plant organisms could not be ascertained with the available information. Therefore, the proposed new lower tiered environmental fate studies are required.

From these case studies the Agency concludes that the proposed approach produces the results desired by the Agency. The proposed approach effectively distinguishes between chemicals that will require more in-depth review and therefore higher-tiered studies versus chemicals that require only the lower tiered environmental fate and ecotoxicity studies to determine that no or few additional higher tiered studies are needed.

The Agency specifically seeks comment on the case studies (Ref. 42) performed, including the assumptions used as model inputs. EPA will consider comments specific to the case studies along with comments on the proposed approach, as the Agency evaluates the use of the proposed approach for down-the-drain antimicrobials in the final rule for antimicrobial data requirements.

E. Hydrolysis Study

EPA proposes to require a hydrolysis study for all antimicrobial pesticides. In 40 CFR part 161, hydrolysis studies are currently required for all use patterns except indoor. (The indoor part 161 use pattern is being considered by EPA to be similar to the low environmental exposure grouping.) Accordingly, EPA proposes to continue to require hydrolysis studies for all of the high environmental exposure use patterns (once-through industrial processes and water systems, antifoulant paints and coatings, wood preservatives, and

aquatic areas) and to codify the requirement for all other antimicrobial use patterns. In practice, hydrolysis studies have been required for all antimicrobial chemicals for over 10 years.

As previously discussed, EPA intends to require the hydrolysis study as part of the lower tier of environmental fate data requirements for down-the-drain chemicals. Chemicals that hydrolyze rapidly to less toxic chemicals may need few higher tiered studies. This study will allow EPA to determine how fast the antimicrobial breaks down in the presence of water and what degradates are formed.

F. Photodegradation in Water

In 40 CFR part 161, the photodegradation in water study is required for aquatic use patterns. The Agency proposes to continue its existing requirement for a photodegradation in water study for the antimicrobial aquatic areas use pattern. The Agency also proposes to require the study for all other antimicrobial uses. This would expand the number of use patterns for which this study is required.

This study will allow EPA to determine the degradation of the pesticide in shallow water bodies as a result of exposure to sunlight. Chemicals that degrade quickly in the environment may need few higher tier studies. As with the data requirements for conventional pesticide chemicals, EPA intends to clarify in a test note certain conditions when photodegradation testing would not be required. Data on photodegradation in water would not be required when the electronic absorption spectra, measured at pHs 5, 7, and 9 of the chemical and its hydrolytic products, if any, do not show absorption or tailing between 290 and 800 nanometers. If no absorption or tailing occurs in this range, it is unlikely that photodegradation occurs (Refs. 25 and 27).

G. Photodegradation in Soil

The Agency is proposing to require the photodegradation in soil study for wood preservatives only. Leaching of wood preservatives (both the parent or transformation products) from preservative-treated wood could contaminate the surrounding soils. This would be a new data requirement which would provide data on the dissipation, nature and persistence of wood preservative degradation products formed by soil surface catalyzed photolysis. Using these data the Agency can assess the extent and duration of human (e.g., children playing below decks) and/or nontarget organism exposures to soils adjacent to preservative-treated wood structures. Such soils may contain the parent compound and/or transformation products, which could include those formed via photodegradation processes.

H. Activated Sludge Sorption Isotherm

The activated sludge sorption isotherm study would be a new data requirement. EPA is proposing to require this study only for the low environmental exposure grouping and the once-through industrial processes and water systems. This study is not required for wood preservatives, antifoulants, or aquatic areas.

For antimicrobial chemicals that go down-the-drain and reach a WWTP, as part of its screening-level environmental fate assessment, EPA will analyze the potential impact of the antimicrobial chemical on the microorganisms in the typical biological treatment processes of a WWTP. The activated sludge sorption isotherm study would allow EPA to assess the distribution of the antimicrobial between the sludge and aqueous phases. This information is important in determining the method used in the ready biodegradability test and the higher-tiered studies that may be required. Antimicrobials that are predominantly in the water column and do not sorb to sludge may not need testing that focuses on sediment and soils, such as the aerobic and anaerobic soil metabolism studies. Antimicrobials that predominantly sorb to the sludge, soil, and sediment may not need testing that focuses on water, such as the aerobic and anaerobic aquatic metabolism studies.

I. Ready Biodegradability

The ready biodegradability study would be a new data requirement. EPA is proposing to require this study only for the low environmental exposure grouping and the once-through industrial processes and water systems. This study is not required for wood preservatives, antifoulants, or aquatic areas.

For antimicrobial chemicals that go down-the-drain and reach a WWTP, as part of its screening-level environmental fate assessment, EPA will analyze the potential impact of the antimicrobial chemical on the microorganisms in the biological treatment processes of a WWTP. Biodegradation is an important environmental pathway in which the antimicrobial is broken down into ''smaller'' chemicals by bacteria. This study supplies information on the rate of breakdown and the completeness of the degradation to carbon dioxide and water. A ready biodegradability study would allow the Agency to determine whether the chemical achieves ''pass levels'' for ready biodegradability (e.g., 70% removal of dissolved organic carbon). These screening tests are so stringent that it is assumed that antimicrobials that ''pass'' will rapidly and completely biodegrade in aquatic environments under aerobic conditions. Chemicals that degrade quickly and completely may need few higher tiered studies.

J. Porous Pot Test

The Agency is proposing to conditionally require the porous pot study for antimicrobials based on the results of the ready biodegradability test. This would be a new data requirement. EPA is proposing to require this study only for the low environmental exposure grouping and the once-through industrial processes and water systems. This study is not required for wood preservatives, antifoulants, or aquatic areas.

The porous pot study simulates the processes in the aeration basin of the activated sludge sewage treatment process. It is therefore a more realistic test than the biodegradability test. A chemical that did not ''pass'' the biodegradability test could degrade (partially or completely) under different conditions. The porous pot study would provide a measure of the extent of biodegradation or removal likely to occur during sewage treatment. An antimicrobial that degrades quickly and completely in a typical wastewater treatment plant may need few higher tiered studies.

K. Modified Activated Sludge, Respiration Inhibition Test

The modified activated sludge, respiration inhibition test would be a new data requirement. EPA is proposing to require this study only for the low environmental exposure grouping and the once-through industrial processes and water systems. This study is not required for wood preservatives, antifoulants, or aquatic areas.

For antimicrobial chemicals that go down-the-drain and reach a WWTP, as part of its screening-level environmental fate assessment, EPA will analyze the potential impact of the antimicrobial chemical on the microorganisms in the biological treatment processes of a WWTP. The modified activated sludge, respiration inhibition test would allow EPA to identify antimicrobials which could harm the microorganisms found in WWTPs and thus impair the ability of these bacteria to carry out their intended function. Additionally, this study would also indicate suitable

concentrations for use in the ready biodegradability test.

L. Leaching and Adsorption/Desorption

In 40 CFR part 161, leaching and adsorption/desorption studies are required for all use patterns except the indoor. Accordingly, EPA proposes to continue to require the leaching and adsorption/desorption studies for all of the high environmental exposure use patterns: Once-through industrial processes and water systems, antifoulant paints and coatings, wood preservatives, and aquatic areas.

EPA is also proposing to conditionally require these data for the low environmental exposure grouping. This would expand the number of use patterns for which the test is conditionally required. For the low environmental exposure grouping, the leaching and adsorption/desorption study is considered to be a higher-tiered study that would be triggered based on a weight-of-evidence evaluation of the results of the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests.

The leaching and adsorption/desorption study would provide information on the mobility of the antimicrobial pesticide in soils. The antimicrobial pesticide may or may not be transported to surface water and/or ground water bodies used for drinking water. The presence of an antimicrobial pesticide in drinking water sources could contribute to exposure via drinking water.

M. Aerobic Soil Metabolism

The Agency proposes to adapt its current requirement in 40 CFR part 161 for an aerobic soil metabolism study to the specific needs of antimicrobial chemicals. Currently, 40 CFR part 161 requires this study for terrestrial and outdoor types of uses.

The aerobic soil metabolism study would be conditionally required for the low environmental exposure grouping, and once-through industrial processes and water systems. This would expand the number of use patterns for which the test is conditionally required. The aerobic soil metabolism study is considered to be a higher-tiered study that would be triggered based on a weight-of-evidence evaluation of the results of the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests.

For aquatic areas, data would be required only for use sites that are intermittently dry. This would codify current practices for aquatic areas.

For wood preservatives, the Agency proposes to require an aerobic soil metabolism study. This would codify current practices for wood preservatives.

The aerobic soil metabolism study would allow EPA to better understand the antimicrobial pesticide's degradation under aerobic (oxygen-rich) conditions in the laboratory. The results of the study would help to determine how fast the antimicrobial degrades in the presence of microorganisms in different natural soils, and what metabolites are formed. Chemicals that degrade quickly in soil are likely to have lower exposure estimates.

N. Anaerobic Soil Metabolism

Due to a printing error, the data requirement for an anaerobic soil metabolism study was inadvertently omitted from the data tables (now in 40 CFR part 161) in 1991, and subsequent publications of the CFR. EPA asserts that this requirement is still in existence: This data requirement was never intentionally removed from the CFR by notice and comment rulemaking, and is not considered a new requirement. Therefore, EPA proposes to adapt its current requirement for an anaerobic soil metabolism study to the specific needs of antimicrobial chemicals by conditionally requiring the study for the low environmental exposure grouping, and wood preservatives.

EPA is expanding the number of use patterns for which the test is conditionally required. For the low environmental exposure grouping, the anaerobic soil metabolism study is considered to be a higher-tiered study that would be triggered based on a weight-of-evidence evaluation of the results of the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests.

For wood preservatives, the anaerobic soil metabolism study would be required if treated wood is used in aquatic environments or in soils which may become flooded or waterlogged. This would codify current practices for wood preservatives.

The anaerobic soil metabolism study would facilitate a better understanding of the antimicrobial pesticide's degradation under anaerobic (oxygen-poor) conditions in the laboratory. The results of the study would help to determine how fast the antimicrobial degrades in the presence of microorganisms in different natural soils, and what metabolites are formed. Chemicals that degrade quickly in soil are likely to have lower exposure estimates.

O. Aerobic and Anaerobic Aquatic Metabolism

In 40 CFR part 161 both the aerobic and anaerobic aquatic metabolism studies are required for aquatic uses. For antimicrobial chemicals, the Agency considers this to include the following uses: Once-through industrial processes and water systems, antifoulant paints and coatings, and aquatic areas. Therefore, the Agency proposes to continue its current requirement for aerobic and anaerobic aquatic metabolism studies for these uses. For wood preservatives these studies have been required on a case-by-case basis; therefore, this proposal would codify current practices.

EPA is also proposing to conditionally require these two studies for the low environmental exposure grouping. This would expand the number of use patterns for which the test is conditionally required..

Anaerobic aquatic metabolism studies describe and measure the formation of pesticide residues in the water column or sediment under low-oxygen conditions. Aerobic aquatic metabolism studies determine the effects that exposure to aerobic, or oxygen-rich conditions in the water column or sediment can have on a pesticide when it is dispersed through the aquatic environment. Since the degradation or dissipation pathways of pesticides in aquatic environments are almost always different from those of terrestrial systems, soil metabolism studies may not clearly define the paths of degradation found in aquatic environments. For the low environmental exposure grouping, the aerobic and anaerobic aquatic metabolism studies are considered to be higher-tiered studies that would be triggered based on a weight-of-evidence evaluation of the results of the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests. Chemicals that degrade quickly in water or sediment are likely to have lower exposure estimates.

P. Aquatic Sediment Studies

Aquatic sediment studies are required for aquatic use patterns in 40 CFR part 161. Accordingly, the Agency proposes to continue its current requirement for aquatic sediment studies for the antimicrobial aquatic areas use pattern. EPA is also proposing to conditionally

require an aquatic sediment study for all other antimicrobial use patterns based on the antimicrobial's potential for aquatic exposure.

For the low environmental exposure grouping, the aquatic sediment study is considered to be a higher-tiered study that would be triggered based on a weight-of-evidence evaluation of the results of the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests. This would expand the number of use patterns for which the test is conditionally required.

For the once-through industrial processes and water systems, antifoulant paints and coatings, and wood preservatives, data would be required based on the potential for aquatic exposure and if the weight-of-evidence indicates that the active ingredient or principal transformation products are likely to have the potential for persistence, mobility, nontarget aquatic toxicity or bioaccumulation. This would codify current practices.

The aquatic field dissipation study is used to determine the nontarget fate of a terrestrially applied pesticide that has a high potential to enter aquatic environments and to substantiate laboratory findings. The laboratory studies address one environmental fate process at a time. The aquatic field dissipation study examines pesticide loss or movement in water and sediment. Under field conditions degradation/dissipation processes can proceed differently from how they occurred under laboratory conditions. Data from this study can reduce the potential overestimation to both exposure and risk that can result from having only laboratory generated data. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

Q. Monitoring of Representative U.S. Waters

The Agency is proposing to conditionally require monitoring of representative U.S. waters for all antimicrobial use patterns. This would include freshwater, saltwater, surfacewater, and groundwater. This would codify current practices.

The Agency would use a weight-of-evidence approach taking into account factors such as available monitoring data; the vulnerability of the freshwater, estuarine, or marine water resources; and the persistence and fate of the pesticide active ingredient (or degradate). Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

Based on past experience, the Agency believes that these monitoring data would be required only for a very small number of antimicrobial pesticide registrations. Monitoring for tributyltin antifoulants of the near coastal waters of the United States including the Great Lakes was required under the Organotin Anti-fouling Paint Control Act of 1988. In 1989, pesticide registrants were required to provide these monitoring data under FIFRA section 3(c)(2)(B). These tributyltin antifoulants data are the only monitoring of representative U. S. waters that has been required for an antimicrobial to date.

R. Special Leaching Study

The Agency is proposing to require special leaching studies for antifoulant paints and coatings, and wood preservatives. Part 161 is not explicit in the data that are currently required because those use patterns are not delineated sufficiently for antimicrobial pesticide chemicals. This proposal would codify the Agency's current practices. These studies are needed because leaching from treated materials is the primary source of environmental exposure to antifoulants and wood preservatives. These studies would provide basic information about the availability of the pesticide to the environment, and would be used to perform exposure and risk assessments.

There is no OPPTS Harmonized guideline for these studies. The applicant may perform the study with a protocol of their choice, or may use the American Wood Preservers' Association's (AWPA) Standard Method of Determining the Leachability of Wood Preservatives (AWPA E11–97), AWPA's Standard Method for Determining the Leachability of Wood Preservatives in Soil Contact (AWPA E20–04), and the American Society for Testing and Materials (ASTM) Standard Test Method for Organotin Release Rates of Antifouling Coating Systems in Sea Water (ASTM D5108–90), or their equivalents. As stated in the test notes to the table in proposed § 158.2280, prior approval by the Agency of studies conducted according to AWPA E11–97 or ASTM D5108–90 is not required. However, all studies that would be conducted according to other protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

XIII. Nontarget Organisms Data Requirements

A. Nontarget Organisms Data Requirements for Antimicrobials

EPA proposes to adapt the basic nontarget organism data types (§ 158.2240) as listed in subpart G of current part 158 to support applications for antimicrobial products. EPA proposes to modify the applicability of those requirements to antimicrobials to reflect differing risks and levels of exposure. Part 161 is not explicit in the data that are currently required because those use patterns are not delineated sufficiently for antimicrobial pesticide chemicals. The proposed table, in § 158.2240, will provide greater transparency and clarity.

Ecological effects testing includes short-term, acute, subacute, chronic, and reproduction studies, which progress from laboratory tests to applied field tests. These data allow the Agency to determine if the standard for registration is met and whether precautionary label statements concerning toxicity or potential adverse effects to nontarget organisms are necessary.

The Agency is proposing to use a tiered system of ecological effects testing to assess the potential risks of pesticide uses to nontarget animals (aquatic and terrestrial vertebrates and invertebrates) for antimicrobial pesticide chemicals. For the first tier of testing EPA proposes to require for all antimicrobial pesticides three types of acute ecological effects studies.

- Avian acute oral LD_{50}.
- Acute freshwater fish LC_{50}.
- Acute freshwater invertebrates EC_{50}.

These acute studies measure toxicity in representative species of the nontarget species most likely to be adversely affected and allow EPA to develop precautionary labeling. Such labeling includes statements such as ''This product is extremely toxic to birds'' or ''This product is toxic to fish.'' These statements provide needed information in case of unintended or co-incident exposure to antimicrobials, such as a transportation accident. And, in fact, these studies are currently required for an application for registration.

These first tier data would be required for all antimicrobial use patterns and performed with the technical grade active ingredient (TGAI). Higher-tiered data would be required when the appropriate trigger in § 158.2240 is met. For instance, results from these first tier studies may indicate the need for acute toxicity testing in an additional species, or higher-tiered studies to assess hazard

to other species or in other parts of the environment. Other factors, such as, toxicity, persistence, and/or potential for bioaccumulation, may indicate the need for higher-tiered ecological effects and environmental fate data. All typical end-use product (TEP) testing is considered to be higher tier. An applicant must carefully consider whether studies listed in the higher tier data requirements are required for registration of his product and should consult with the Agency, as needed.

The Agency has divided the antimicrobial pesticides into two groups for determining ecological effect data requirements, based on their expected environmental exposure. The two groupings are the same groupings used for environmental fate data requirements: Low and high environmental exposure groupings. (see Unit XI.B of this preamble.)

B. The Low Environmental Exposure Grouping

The use patterns within this grouping are the same as those described in Unit XI.B. of this preamble for environmental fate data requirements. As previously discussed in this Unit, EPA proposes to require a first tier of three ecological effects studies for all antimicrobials. These three acute ecotoxicity studies in combination with the screening-level environmental fate assessment proposed to be required for assessing the impacts of antimicrobial pesticides on WWTPs, are the initial studies for environmental modeling for risk assessment purposes. For the low environmental exposure grouping, higher-tiered ecotoxicity studies are conditioned on a weight-of-evidence evaluation of the results of the tier one ecotoxicity studies and/or the results of the screening-level environmental fate assessment. Thus, the studies described in Unit XIII.F., G., I., J., K., L., and M. could be triggered.

C. The High Environmental Exposure Grouping

As with the environmental fate data requirements, the high exposure environmental group consists of the once-through industrial processes and water systems, antifoulant paints and coatings, aquatic areas, and wood preservatives. These uses either occur outdoors, discharge effluent directly to the outdoors, or result in materials treated with antimicrobials (e.g., wood preservatives and antifoulants) being placed in the environment, thereby leading to potentially significant environmental exposure. For the high environmental exposure grouping, EPA proposes to require three first tier ecological effects studies and depending on the use pattern, other ecotoxicity studies such as avian studies and TEP testing. The Agency may require additional ecotoxicity studies based on the results of these studies or on other information.

D. Acute Avian Oral Toxicity

In 40 CFR part 161 acute avian studies are conditionally required for ''indoor'' uses of antimicrobials, and are required for aquatic uses of antimicrobials. (The indoor part 161 use pattern is being considered by EPA to be similar to the low environmental exposure grouping.) The Agency is proposing to require submission of acute avian LD_{50} toxicity studies for all antimicrobial use patterns. These studies are needed as part of the tier one ecotoxicity testing, and as previously explained are used to develop precautionary labeling.

Testing in one avian species is required for the low environmental exposure grouping. The shift from CR to R for the low environmental exposure grouping would expand the number of use patterns for which this study is required.

For antimicrobial chemicals, the Agency considers the aquatic use pattern in part 161 to include the following antimicrobial use patterns: Once-through industrial processes and water systems, antifoulant paints and coatings, and aquatic areas. Therefore, the Agency proposes to continue its current requirement for acute avian oral acute toxicity studies for these uses. For wood preservatives these studies have been required on a case-by-case basis; therefore, this proposal would codify current practices.

As with the data requirements for conventional pesticide chemicals, the Agency is proposing to change the testing requirement from one species to two species for all antimicrobial use patterns except the low environmental exposure grouping. The change to two species is consistent with the Agency's current practices.

The species proposed in this proposal differ from those in the requirements for conventional pesticides. Many conventional chemicals are applied outdoors and are considered to be terrestrial uses. For antimicrobials the Agency is proposing that the testing be conducted with a waterfowl species and an upland game bird species. The selection of waterfowl and upland game species is consistent with the current submissions by registrants of antimicrobial products and reflects the data needed for the many indoor and aquatic uses of antimicrobials.

E. Acute Aquatic Toxicity Studies

The Agency is proposing to require acute aquatic toxicity studies (LC_{50} fish and EC_{50} invertebrate) for all antimicrobial uses. These studies are needed as part of the tier one ecotoxicity testing, and as previously explained are used to develop precautionary labeling.

1. *Tier 1 testing.* In part 161, acute aquatic toxicity studies are conditionally required for ''indoor'' uses of antimicrobials, and are required for aquatic uses of antimicrobials.

For antimicrobial chemicals, the Agency considers the aquatic use pattern in part 161 to include the following uses: Once-through industrial processes and water systems, antifoulant paints and coatings, and aquatic areas. Therefore, the Agency proposes to continue its current requirement for two acute aquatic fish toxicity studies (one warm water and one cold water species) and one invertebrate toxicity study for these use patterns. For wood preservatives these three studies have been required on a case-by-case basis; therefore, this proposal would codify current practices.

For the low environmental exposure grouping, the Agency is proposing to require the acute freshwater fish toxicity study in one species, either a warm water or a cold water species. Testing on a second species is required if the active ingredient or principal transformation products are stable in the environment or if the LC_{50} in the first species tested is greater than 1 part per million (ppm) or 1 milligram/liter (mg/L). This would codify existing practices. Additionally, the shift from CR to R for the low environmental exposure grouping (which contains many of the ''indoor'' uses) would also codify current practices.

2. *TEP testing.* Typical End-Use Product (TEP) testing is proposed for both the acute freshwater fish and invertebrate toxicity studies. This is an existing requirement according to the test notes to the table in § 161.490.

F. Avian Dietary Toxicity

Currently in part 161 an avian dietary LC_{50} study is conditionally required for the greenhouse and indoor use patterns and required for all other use patterns. Today the Agency is proposing to continue this existing requirement by requiring the avian dietary study for aquatic areas and conditionally requiring the study for all other antimicrobial use patterns.

G. Avian Reproduction

The Agency has adapted the current data requirements in part 161 for avian

reproduction testing to determine the avian reproduction data requirements for antimicrobial chemicals. An avian reproduction study is conditionally required for aquatic uses in part 161.

The Agency is proposing to require the avian reproduction study for the antimicrobial aquatic areas use pattern. The proposed change from conditionally required to required is consistent with the Agency's current practices.

For all other antimicrobial use patterns, the Agency is proposing to conditionally require the avian reproduction study. For wood preservatives this study has always been considered when EPA made its case-by-case determinations on the data needed for risk assessment; therefore, this proposal would codify the current practices used for wood preservatives. Since part 161 conditionally requires this testing for ''aquatic uses,'' the Agency's proposal continues the existing data requirement for the once-through industrial processes and water systems. Since the testing is also proposed to be conditionally required for the low environmental exposure grouping, this would expand the number of use patterns for which these studies are conditionally required.

H. Acute Estuarine and Marine Study

Acute estuarine and marine toxicity studies are performed on three species: An estuarine/marine mollusk, an estuarine/marine invertebrate, and an estuarine/marine fish. These studies measure toxicity in representative estuarine and marine species of the nontarget species most likely to be adversely affected.

1. *TGAI testing.* The Agency is proposing to require these three acute estuarine and marine studies for antifoulant paints and coatings, and conditionally require these studies for wood preservatives. This would codify the Agency's current practices.

Testing for all other antimicrobial use patterns would also be conditionally required. The Agency is proposing in part 158, subpart W to use the same conditionalities (as described in the test notes) for requiring these studies as in part 161, i.e. the testing is required if residues from the parent compound and/or transformation products are likely to enter the estuarine/marine environment.

Part 161 conditionally requires this testing for ''aquatic uses.'' Therefore, the Agency's proposal continues the existing data requirement for the once-through industrial processes and water systems, and aquatic areas. Since the testing is also proposed to be conditionally required for the low environmental exposure grouping, this would expand the number of use patterns for which these studies are conditionally required.

2. *TEP testing.* For the acute estuarine and marine studies, TEP testing is proposed to be conditionally required for the low environmental exposure grouping, once-through industrial processes and water systems, and aquatic areas. This is an existing requirement according to the table in § 161.490.

I. Fish Early Life Stage and Aquatic Invertebrate Life-Cycle Study

The Agency proposes in § 158.2240 to require both a fish early life stage and an aquatic invertebrate life-cycle study for once-through industrial processes and water systems, antifoulant paints and coatings, and aquatic areas. For these use patterns this would codify current practices.

The Agency also proposes to conditionally require both studies for the low environmental exposure grouping. This would expand the number of use patterns for which the test is conditionally required.

The Agency proposes to conditionally require both studies for wood preservatives. The studies would be required if pesticide residues from treated wood would be likely to enter freshwater or estuarine/marine environments, as determined by the Agency.

Currently, in part 161 only one of these studies is conditionally required. Part 161 requires the submission of either the fish early life stage or the aquatic invertebrate life-cycle study, based on the more sensitive of the two species, as determined by the acute ecotoxicity studies. However, since both fish and invertebrates may be exposed when an antimicrobial pesticide enters natural waters, the Agency now believes both studies are needed. Neither study would adequately substitute for the other. While data from acute invertebrate and acute fish studies would be available, EPA does not believe that these acute studies would predict chronic sensitivity.

For the low environmental exposure grouping the requirements are triggered if antimicrobial pesticide residues from the parent compound and/or transformation products are likely to enter freshwater or estuarine/marine environments, as determined by the Agency. For wood preservatives the requirements are triggered if antimicrobial pesticide residues from the parent compound, transformation products, and/or leachates from preservative-treated wood are likely to enter freshwater or estuarine/marine environments, as determined by the Agency.

J. Fish Life Cycle

Currently, this existing data requirement is conditionally required for all antimicrobials except ''indoor'' uses in part 161. The Agency is now proposing to expand this conditional requirement to all antimicrobial use patterns.

The fish life cycle study is a two generation reproductive study in fish that can characterize a number of sensitive life stages. Just as with conventional pesticide chemicals, it is triggered on the results of the fish early-life stage or invertebrate life cycle test, or other information indicating the reproductive physiology of fish may be affected. For the low environmental exposure grouping, the screening-level fate assessment would also inform the determination to require this study. If the antimicrobial is not degraded by the processes in the WWTP and is in the effluent released to surface water, then this study may be required.

K. Aquatic Organisms, Bioavailability, Biomagnification Toxicity Tests

This data requirement is composed of three studies: The oyster bioconcentration factor, the fish bioconcentration factor, and the aquatic food chain transfer. All three studies are not needed for every antimicrobial. The most commonly submitted study is the fish bioconcentration factor.

Currently, these studies are conditionally required for all antimicrobials except ''indoor'' uses in part 161. The Agency is now proposing to expand this conditional requirement to all antimicrobial use patterns. For the low environmental exposure grouping, the screening-level fate assessment would also inform the determination to require this study. If the antimicrobial is not degraded by the processes in the WWTP and is in the effluent released to surface water, then this study may be required.

For antimicrobials that have the potential to reach freshwater or saltwater, these studies are needed to identify those antimicrobials that could concentrate in various aquatic taxa. EPA is proposing to clarify in the test notes the three specific circumstances under which the study is not required. These three circumstances are the same as in the final rule for conventional pesticide chemicals.

L. Simulated or Actual Field Testing for Aquatic Organisms

For all antimicrobial use patterns, the Agency is proposing to conditionally require simulated or field studies for aquatic organisms. These studies would be triggered when under actual use conditions significant impairment of nontarget aquatic organisms is likely to occur in the natural environment. This proposal would codify current practices.

The Agency currently determines whether simulated or field studies are required for antimicrobials on a case-by-case basis, considering information such as:

- The pesticide's intended use.
- The pesticide's use rates.
- The pesticide's toxicity.
- The pesticide's physical and chemical properties.
- The parent compound's environmental fate characteristics and transformation products (such as metabolites and degradation products).
- Nontarget organisms likely to be exposed.
- Likelihood of exposure.

As with conventional pesticides, the Agency is proposing to require independent laboratory validation of the environmental chemistry methods used to generate the data associated with this study.

M. Sediment Testing

The Agency is proposing to require acute invertebrate sediment testing, both freshwater and marine, for antifoulant paints and coatings and to conditionally require these studies for once-through industrial processes and water systems, wood preservatives, and aquatic areas. This would codify current practices. Additionally, EPA proposes to expand the conditional requirement to all other antimicrobial use patterns. This study would be triggered based on the antimicrobials presence in the water column (for example when released from a WWTP), the potential to sorb to sediment, and the persistence of the antimicrobial.

The Agency is proposing to conditionally require chronic invertebrate sediment testing, both freshwater and marine, for all antimicrobial use patterns. This study is triggered by the same criteria as the acute sediment study, but would be of longer duration as determined by the persistence of the antimicrobial. This conditional requirement would codify current practices for the high environmental exposure grouping, and would then expand the requirement to the low environmental exposure grouping.

Testing of aquatic organisms exposed to treated sediments allows EPA to assess the effects of sediment-bound pesticide residues in aquatic environments. The effects of sediment-bound pesticides (or their degradates) on aquatic environments cannot be accurately assessed from bioassays on compounds suspended in the water column alone. For example, lipophilic or hydrophobic chemicals can dissipate from the water column, but may remain in the aquatic environment adsorbed to sediment. As discussed in the proposed rule for conventional pesticides (70 FR 12275) sediment-bound pesticides may differ significantly from pesticides in solution, showing different physical, chemical, and biological properties, chemical partitioning, bioavailability, concentrations in interstitial or pore water, exposure from sediment ingestion and possible manifestations of food chain effects. By serving as a potential pesticide sink, exposure to these compounds may lead to significant environmental risk to a wide variety of fish and aquatic invertebrates which live and feed at the bottom of a lake or stream. Sediment toxicity testing is needed to assess the bioavailability of a sediment-bound compound and to characterize the possible impact to sediment-dwelling benthic organisms.

Once the Agency determines or extrapolates that the use pattern has the likelihood for chemical exposure to an aquatic system, then the available information on the adsorption of the chemical is reviewed. If the Agency determines that the antimicrobial meets one or more of the criteria for adsorption, then the available information on persistence of the chemical is reviewed. If one or more of the criteria for persistence are met, then a sediment study is required. Persistence (half-life of the pesticide in sediment) drives the decision regarding whether the acute or chronic study is conducted.

Before designing the protocol, consultation with the Agency is needed if the applicant is uncertain as to which length of study is appropriate. For certain antimicrobials that are highly persistent, only the chronic study may be required. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

N. Honeybee Protection

The current data requirements for testing pesticide toxicity to honeybees at § 161.590 require the honeybee acute contact LD_{50} study when honeybees are likely to be exposed. The Agency proposes to conditionally require the acute study for wood preservatives and the low environmental exposure grouping. Since the study would be required only for uses involving treatment of beehives, empty or occupied, and since there are few such uses for antimicrobials, this study would be infrequently required. This study may not be required if the use pattern (as described on the label) prohibits fumigating or spraying beehives.

Since beehives can be constructed of materials that have been treated with antimicrobials, the Agency proposes to conditionally require a study to determine the toxicity of treated wood and other materials to bees. This study must be conducted in a manner similar to that of the Honey Bee Toxicity of Residues on Foliage. This would codify current practices. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

XIV. Plant Protection Data Requirements

A. Plant Protection Data Requirements

EPA proposes to adapt the basic nontarget plant protection data types as listed in 40 CFR part 158, subpart G to support applications for antimicrobial products. EPA proposes to modify the applicability of those requirements to antimicrobials to reflect differing risks and levels of exposure. Part 161 is not explicit in the data that are currently required because those use patterns are not delineated for antimicrobial pesticide chemicals. The proposed table in § 158.2250 will provide greater transparency and clarity.

Plants represent the most basic component of any functioning ecosystem by providing oxygen and a food source for aquatic and terrestrial animals. Therefore, it is important to determine the toxicity of the antimicrobial to plants. The data obtained from these studies will be used to conduct nontarget plant risk assessments. For aquatic environments such an assessment could include an effluent from a wastewater treatment plant being released into the environment. For terrestrial environments such an assessment could include wood preservatives in contact with soil, land-application of biosolids, or antimicrobials that partition to soil and sediment.

B. Requirement for Tier II Testing for Antimicrobials

The Agency's guidelines for conducting nontarget plant protection

studies specify two types of tests: Single-dose studies (referred to in the guidelines as Tier I tests) and multiple-dose studies (Tier II). Usually, the applicant would conduct the single-dose studies first, and then, based on the results of the single-dose studies, proceed to the multiple-dose studies, which evaluate the effects of multiple dosage levels on plant growth and are used to determine acute toxicity levels in comparison with environmental concentrations. Such studies are used to estimate the risk to nontarget plants and endangered plant species.

Many antimicrobial pesticides are used to control plant pests such as algae in industrial processes (paper making, cooling towers, wastewater, sewage water treatment), and residential uses (swimming pools, ornamental ponds, moss growing on roofs). Some antifoulants, ballast water treatments, and wood preservatives are also intended to control plant pests. Therefore, antimicrobial pesticides used for plant pest control are expected to be phytotoxic to nontarget plants once released into terrestrial or aquatic environments.

Accordingly, for all antimicrobial use patterns, the Agency is proposing only to require multiple-dose studies, which is consistent with the testing of certain phytotoxic conventional chemicals such as herbicides which also start at Tier II. In part 161, for most plant studies, the Tier II study is conditionally required and the Tier I study is required. For antimicrobials, EPA believes that the nontarget plant studies have been interpreted in the context of, and consistent with other phytotoxic chemicals, and this proposal would codify the shift from the use of the Tier I study to a Tier II study.

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. The Agency can evaluate the information and inform the applicant as to the sufficiency, or the need for multiple-dose studies. If the applicant does not have any studies, then multiple-dose studies must be conducted.

C. The Low Environmental Exposure Grouping

The use patterns within this grouping are the same as those described in the Unit XI.B. of this preamble for environmental fate data requirements.

D. The High Environmental Exposure Grouping

The use patterns within this grouping are the same as those described in the Unit XI.B. of this preamble for environmental fate data requirements.

E. Seedling Emergence (Tier II – Dose-Response)

This terrestrial plant toxicity test is designed to evaluate toxicity to germinating seedlings and their ability to survive after chemical uptake from the surrounding soil. The Agency is proposing to require this study for the high environmental exposure grouping. This proposal would codify the shift from the use of the Tier I study to a Tier II study and thereby would codify current practices.

The Agency is also proposing to conditionally require the Tier II study for low environmental exposure grouping based on the results of the algal study. This would expand the number of use patterns for which this study is conditionally required.

F. Vegetative Vigor (Tier II – Dose-Response)

This terrestrial plant toxicity test is designed to evaluate toxicity to young plants. The antimicrobial is applied to the foliage to evaluate uptake of the antimicrobial from the exposed green tissue. The Agency is proposing to require this study for wood preservatives and aquatic areas. For wood preservatives, this would codify current practices. For aquatic areas, this would codify the shift from the use of the Tier I study to a Tier II study and thereby would codify current practices.

The Agency is also proposing to conditionally require this study for the low environmental exposure grouping, and industrial processes and water systems (once-through). This would expand the number of use patterns for which this study is conditionally required.

G. Aquatic Plant Growth (Lemna gibba) (Tier II – Dose-Response)

The Agency is proposing to require the Aquatic Plant Growth (*Lemna gibba*) (Tier II – Dose-Response) study for the high environmental exposure grouping. This would codify the shift from the use of the Tier I study to a Tier II study and thereby would codify current practices.

The Agency is also proposing to conditionally require the Tier II study for low environmental exposures based on the results of the algal study. This would expand the number of use patterns for which this study is conditionally required.

Lemna gibba or duckweed is an important wildfowl food source and is used in wastewater reclamation. Therefore, it is important to understand the impact of an antimicrobial on this food source.

H. Aquatic Plant Growth (Tier II – Dose-Response)

The Agency is proposing to require one or more of the Aquatic Plant Growth (Tier II – Dose-Response) studies for all antimicrobial use patterns. As with the aquatic plant study discussed in the previous section, part 161 requires the Tier I study and conditionally requires the Tier II study. For the high environmental exposure grouping, this would codify the shift from the use of the Tier I study to a Tier II study and thereby would codify current practices. Testing is required for four species representing green algae, freshwater cyanobacteria, a freshwater diatom and a marine diatom. These four species are used to represent hundreds of different species.

Testing is required in only one species (green algae) for the low environmental exposure grouping. This would expand the number of use patterns for which this study is required.

Green algae produce oxygen, serve as a food source for aquatic animals, and provide the basic energy needs of any aquatic ecosystem. The results of the green algae study will allow the Agency to determine if the other three aquatic plant growth studies are required for the low environmental exposure grouping.

I. Terrestrial and Aquatic Field Studies

The Agency is proposing to conditionally require Terrestrial and Aquatic Field Studies for all antimicrobial use patterns. Field studies provide more realistic information on a pesticide's impacts than laboratory studies which focus only on one parameter, because field studies consider all potential impacts on plant growth. The need for these higher tier studies would be based on the results of the lower tier plant protection studies, adverse incident reports, intended use pattern, and environmental fate characteristics that indicate potential exposure.

These two studies are conditionally required in part 161 for three use patterns. Due to the use patterns currently used in part 161, there is not sufficient delineation for comparison to the antimicrobial use patterns proposed today. While EPA routinely considers the need for these studies in determining the data needed for its risk assessments, it has required these

studies based on case-by-case circumstances on a very infrequent basis for antimicrobials.

Since the testing is proposed to be conditionally required for all antimicrobial pesticide use patterns, this would expand the number of use patterns for which these studies are conditionally required. Additionally, this would harmonize the requirements for antimicrobials with those of conventional pesticides.

XV. Peer Review

A. National Research Council Recommendations

The National Academy of Sciences issued a report in 1993 entitled, ''Pesticides in the Diets of Infants and Children'' (Ref. 19). The study, conducted by the National Research Council (NRC), was initiated to address the question of whether the current regulatory system adequately protected infants and children from pesticide residues in food. The Council reviewed EPA's then-current practices and data requirements related to dietary risk assessment as well as testing modifications planned by the Agency. The panel of experts concluded that, at that time, EPA approaches to data requirements and risk assessments emphasized the evaluation of the effects of pesticides in mature animals and, in general, there was a lack of data on pesticide toxicity in developing organisms.

The Council's recommendations with respect to regulatory needs for data development included the following:

- Discussed the need to investigate the effects of pesticide exposure on immunotoxic responses in infants and children.
- Supported the need for acute and subchronic neurotoxicity testing and encouraged the Agency to have these studies as part of the required data for all food-use pesticides.
- Encouraged further work in the area of developmental neurotoxicity.

Many of the NRC recommendations were incorporated into the data requirements that were promulgated for conventional pesticides (72 FR 60933), and for biochemical and microbial pesticides (72 FR 60988). By deliberately building on the foundation of these promulgated rules, and harmonizing to the extent practicable considering the differences in use patterns, many of the NRC recommendations, such as immunotoxicity testing, are incorporated into this proposed rule for antimicrobial pesticides.

B. FIFRA Scientific Advisory Panel (SAP)

1. *1994 meeting*. In 1994, EPA held a 2–day meeting of the SAP to review the Agency's proposed amendments to the data requirements for pesticide registrations contained in 40 CFR part 158, which covered antimicrobials. The SAP was asked to comment on each data requirement and identify, in their scientific opinion, which requirements were necessary to fully and thoroughly evaluate the potential hazard of a chemical compound and which were not intrinsically useful in providing practical scientific information. The revisions presented to the Panel, i.e., the changes to the data requirements presented in this document, were generally endorsed. A very complete discussion of the 1994 SAP meeting was presented in the proposed rule for conventional pesticides (70 FR 12276).

2. *June 1997 meeting: A set of scientific issues being considered by the Agency to determine antimicrobial issues*. On June 3, 1997, the Agency presented an early version of the part 158, subpart W proposal in an open meeting to the SAP. The Agency asked for specific comments in five areas covered by proposed 158W data requirements: Toxicology; residue chemistry, ecological effects and environmental fate, human exposure, and efficacy. The SAP's full comments are found in the docket for this action (Ref. 29) and are summarized here.

i. *Toxicology*. The Agency asked if its division of antimicrobial pesticide uses into high human exposure and low human exposure groups, with extensive data requirements for high exposure uses and tiered data requirements for low exposure uses, was an acceptable approach. The SAP agreed that the Agency's tiered approach was reasonable, and made several suggestions to improve the proposal. Two of these suggestions were ''unambiguous trigger points indicating next Tier level of toxicity testing,'' and ''to continue dialogue with Canadian counterparts to harmonize, clearly define trigger points, and improve the guidelines.''

The Agency has worked to provide clear, unambiguous triggers in the test notes to the toxicology data requirements tables. EPA is also committed to dialogue with its Canadian counterpart. PMRA has routinely received updates on the status of the draft antimicrobial data requirements, and has been actively engaged throughout the development of this proposal.

ii. *Residue chemistry.* The Agency asked the SAP if the scientific approach to obtaining dietary residue information in general, but specifically for indirect food contact sanitizers, was reasonable. The SAP agreed that the scientific approach was reasonable, and remarked extensively on the residue chemistry data requirements for indirect food uses such as sanitizers. They noted that such products had generally been of low toxicity or low persistence, and their belief that a tolerance or tolerance exemption for such uses was unnecessary, based on FDA's practice with such products. The SAP also suggested the use of default surface residue values for estimating sanitizer residues to obviate the need for measured data.

Although the SAP believes that a tolerance or tolerance exemption is unnecessary, under FFDCA, EPA is required to establish either a numerical tolerance, or an exemption from the requirement of a tolerance for indirect food uses. To obviate the need for measured data, EPA uses modeling and ''worst-case'' estimates, as appropriate. As discussed in Unit X. of this preamble, if such estimates when paired with the toxicity data do not indicate a concern, then it is unlikely that measured surface residue data would be required.

iii. *Human exposure.* The Agency asked the SAP if the approaches presented were reasonable and if the Agency had adequately accounted for all antimicrobial use and exposure scenarios. Additionally, the Agency asked if multiple exposure scenarios for one pesticide product would be better accounted for by data for all applicable exposure scenarios or a subset of applicable scenarios.

- The SAP agreed that the Agency's 12 use categories for antimicrobials were a reasonable approach to organizing exposure data requirements, and were, in fact, similar to the approaches used by PMRA and the California EPA. EPA is proposing that these use categories be codified in § 158.2201 as the antimicrobial use patterns.
- The SAP also advised that initially, all applicable exposure scenarios should be considered for a single antimicrobial product. The Agency accepted this recommendation which is now part of its standard exposure assessment practices.
- The SAP expressed concern that post-application exposure might be too narrowly defined, and noted some possible exposure scenarios involving persons not in the 1997 presentation. In response, the Agency has broadened the scope of post-application exposure to

include persons who may come in contact with materials after treatment. This includes contact with impregnated materials and children's exposure to treated wood. In response, the Agency is proposing to require the indoor surface residue dissipation study and the non-dietary ingestion exposure study for residential uses to address this concern.

iv. *Ecological effects and environmental fate*. For the 1997 presentation to the SAP, EPA divided the antimicrobial use sites into two groupings: high expected environmental exposure and low expected environmental exposure. The Agency asked if a tiered data set to support an ecological risk assessment for uses with high expected environmental exposure was appropriate. The SAP agreed that a tiered data set to support an ecological risk assessment would be appropriate.

EPA also asked if ecological risk assessments were necessary for the low expected environmental exposure grouping. In its presentation EPA stated its intention to require a very reduced data set suitable for developing precautionary labeling for manufacturing and certain end-use products. At that time EPA considered that ''indoor'' uses had minimal environmental exposures or releases of pesticide residues to the environment. The SAP commented that the reduced data set could be justified only if data available from other programs within EPA and elsewhere were adequate to assess ecological risk. As a result of the SAP's concerns, the Pesticide Program discussed these issues with EPA's Office of Solid Waste and Office of Water.

As a result of these discussions in the late 1990s, the Pesticide Program continued to believe that

- ''Indoor'' residential uses of antimicrobials with the rinses going down-the-drain had minimal environmental exposures or releases of pesticide residues to the environment,
- Industrial effluents that could possibly contain antimicrobials would be adequately regulated via the permitting process under the National Pollutant Discharge Elimination System Program of the Clean Water Act and wastes possibly containing antimicrobials would be adequately regulated under the Resource Conservation and Recovery Act.

Therefore, in 1997, the Agency determined not to require biodegradation or microbial data.

More recently, as part of its development of this proposed rule, EPA re-evaluated its belief that ''indoor'' residential uses had minimal environmental exposures. EPA is now proposing to require the environmental fate and ecological effects data for conducting an ecological risk assessment for down-the-drain antimicrobials. The rationale for this decision is discussed in Unit XII.B. of this preamble.

The SAP expressed its concerns about ''the lack of chemical fate data,'' and also stated that biodegradation data (both aerobic and anaerobic) should be required.

- In response to the SAP, EPA reexamined the need for environmental fate data other than hydrolysis, and as a result of this 1997 reexamination, the Agency determined to conditionally require data on photodegradation in water for these low expected environmental exposures. EPA is now proposing to require the photodegradation in water study for all antimicrobial chemicals, including the low environmental exposure grouping.
- Initially, in 1997, the Agency determined to not require biodegradation data. EPA has reconsidered this 1997 decision and today is proposing to require an activated sludge sorption isotherm, a ready biodegradability test, and a modified activated sludge, respiration inhibition study for the low environmental exposure grouping.

The SAP also questioned why microbial data to protect publicly owned treatment works (POTWs) and other treatment systems which often rely on microbial treatment processes were not required. The Agency investigated this possibility, but could not in the early 1990s determine a satisfactory set of data that would then be useful in protecting the highly variable conditions of specific POTWs. EPA is proposing as part of its environmental fate data requirements, to require the data that would allow EPA to assess the impacts of antimicrobials on wastewater treatment plants.

The SAP questioned the use of precautionary labeling to protect fish and wildlife from improper use of antimicrobials, especially considering that some use categories would pose exposure via sewage systems. As a result, EPA prepared sample labeling to reduce this source of exposure: ''This product is toxic to fish and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or public water unless this product is specifically identified and addressed in a NPDES permit. Do not discharge effluent containing this product to sewer systems without previously notifying the sewage treatment plant authority.'' This type of labeling is still in use today.

The SAP cautioned that although wildlife exposure to antimicrobials via water was the most likely source of exposure, terrestrial exposure is also possible. The Agency concurred, and is proposing to require for the aquatic areas use pattern and to conditionally require for all other use patterns, the avian dietary and avian reproductive studies for performing such an assessment.

Finally, the SAP expressed concern that antimicrobial metabolites may be more toxic than their parent compounds, and therefore may also need to be tested. The Agency agrees, and has revised many of the test notes in this proposal to clarify the need for data on metabolites when the available information demonstrate that the metabolites are more toxic or otherwise pose environmental risks.

3. *1998 and 1999 meetings*. Data requirements, as related to the application of the newly mandated FFDCA safety factor (required under the FQPA amendments) were presented to the SAP in 1998 and 1999. Copies of documents prepared for the 1998 and 1999 SAP meetings and the final reports from each of the meetings are in the docket for this action (Refs. 30, 31, 32, and 33) and can be found on EPA's web site at *http://www.epa.gov/scipoly/sap*. A summary of the issues specific to the proposed antimicrobial data requirements follows:

i. *Toxicology*. In December 1998, EPA presented the SAP an issues paper on the use of the FQPA safety factor to address the special sensitivity of infants and children to pesticides. The discussion on the developmental neurotoxicity study was specifically discussed in the context of the appropriateness of using an additional safety factor. At that time, the SAP did not reach a consensus recommendation on whether this study should be routinely or conditionally required. The issue of what is a complete and reliable data set was brought before the SAP again in May 1999. The majority of the Panel supported the Agency's approach to applying data requirements but advised the Agency to revisit the first tier of required toxicity studies every few years to update data requirements as needed. The Panel also agreed with the Agency on the need to require the neurotoxicity battery of studies, including developmental neurotoxicity testing, for high exposure pesticides such as food-use pesticides. The SAP's recommendations are reflected in today's proposed antimicrobial data requirements for developmental neurotoxicity and immunotoxicity. This also harmonizes the data requirements

for conventional pesticides and for antimicrobials.

ii. *Post-application exposure.* Working in collaboration with Health Canada and the Organization for Economic Cooperation and Development (OECD), EPA drafted guidelines for post-application exposures studies. They were internally peer-reviewed and shared with the California Department of Pesticide Regulation, representatives from academia, and the American Crop Protection Association. The Agency presented its post-application exposure guidelines and standard operating procedures to the SAP in 1998 and again in 1999. In 1999, the SAP commended the Agency for making significant strides toward developing scenario-based residential and non-occupational exposure assessments that are sufficiently conservative as to not underestimate exposures. The data requirements proposed for post-application exposure to antimicrobials are drawn from this body of work.

4. *2000 meeting.* In its response to an April 2000 presentation on certain scientific issues concerning probabilistic ecological risk assessment, the SAP was asked for recommendations on sediment toxicity testing. The SAP stated that the extent to which a compound partitions from the aqueous phase to the sediment is a key consideration in determining the need for testing benthic organisms. There was a consensus among SAP members that compounds with high K_{oc}s (organic carbon-water partition coefficient) or K_{ow}s (octanol-water partition coefficient) required sediment testing for benthic fish or invertebrates. A copy of the final report is in the docket for this action (Ref. 34) and can be found on EPA's web site at *http://www.epa.gov/scipoly/sap*. Based on this meeting, the guidelines for sediment testing were developed. For antimicrobials, acute and chronic sediment testing are proposed to be required or conditionally required.

XVI. International Activities

EPA actively works through international and regional organizations and directly with other countries to develop common or compatible international approaches to pesticide registration, including data requirements. Joint reviews and work sharing are two of the approaches used by EPA to increase the harmonization of pesticide regulatory programs. EPA believes that making pesticide regulatory programs more consistent internationally will:

- Maintain high standards for the protection of human health and the environment.
- Increase the efficiency of the registration process by lessening the resource burden on governments and the regulatory community.
- Provide more equal access to pest management tools.
- Strengthen the regulatory process.
- Facilitate the registration of alternative pest control tools.
- Minimize trade problems.

Harmonization activities are increasing and evolving as agencies and applicants build upon their experiences.

A. Joint Data Reviews and Evaluations

EPA is working closely with other countries toward greater uniformity in testing, reviewing and evaluating all pesticides. The benefits of international regulatory cooperation on antimicrobials are potentially great: Improved science through greater information exchange, and reduced regulatory and resource burdens on national governments and regulated parties through harmonized pesticide regulatory review. Over the last several years, substantial progress has been made toward international cooperation on pesticide regulatory review. Member countries of the Organization for Economic Cooperation and Development (OECD), including the United States, have agreed upon harmonized guidance for the formats of industry data submissions (dossiers) and country data review reports (monographs). Countries now frequently exchange pesticide reviews or consult with one another on key technical aspects of a review.

Under the North American Free Trade Act (NAFTA), EPA has worked cooperatively with Canada and/or Mexico, dividing up detailed evaluation work on a number of pesticides. The Agency has also entered into similar information exchange and comparative review arrangements with other countries. There have been multiple bilateral joint reviews and/or work sharing with member countries of the European Union. Trilateral joint reviews and workshares have been performed with Canada and Australia. A global joint review is being conducted among six countries (the United States, Australia, New Zealand, Canada, Ireland, and the United Kingdom.) The peer reviewers will be four other EU countries. The primary objective of all of these arrangements has been to use resources in the most efficient way possible.

Concerning antimicrobials, since 2000, Health Canada's Pest Management Regulatory Agency (PMRA), the USEPA and California's EPA have been cooperating on a joint review for the re-evaluation/reregistration of the following three heavy-duty wood preservatives: Pentachlorophenol, creosote, and chromated copper arsenate. The review of submitted data, writing of the risk assessments, and peer review activities are being shared. Exposure data used in the preliminary risk assessment were collected from both U.S. and Canadian wood-treatment facilities. Both PMRA and EPA are contributing to the public comment process. The cooperative activities continue as both EPA and PMRA work toward issuance of their decision documents in September 2008.

B. Harmonization of Data Requirements

As the international regulatory community works toward greater harmonization on pesticide review, attention has also focused on the data requirements, how the requirements compare from one country to another, and what can or should be done to establish common requirements. To the extent that data requirements for pesticide registration are similar, sharing reviews and comparing evaluations is easier and more meaningful. Requirements that differ considerably from one country to another can mean that applicants who are looking to register a pesticide in more than one country may have to conduct many different studies to satisfy all the various national requirements. Therefore, from the perspective of the applicant, establishing similar requirements also can reduce the resources that must be spent to conduct testing.

OECD Member countries have had discussions about harmonizing pesticide data requirements within the OECD community. The pesticide industry took on the complex task of looking at data requirement differences among Member countries to identify areas that might benefit from harmonization. Preliminary findings presented to the OECD Working Group on Pesticides Meeting in June 2001, reported, consistent with the positions of scientific reviewers in OECD Member countries, that toxicology data requirements are quite similar across countries. This does not mean that there is no room for additional harmonization work on toxicology data requirements, but rather that there are other testing areas where there is much less consistency on data requirements across countries.

Ecotoxicological and environmental fate studies present a particular

challenge for harmonization. Data requirements in these areas can differ considerably from one country to another depending upon how countries' tiered approaches to data requirements are applied. National data requirements must be tied to national use patterns and environmental and ecological conditions. A reliable environmental hazard assessment, for example, must be based on studies that accurately reflect the climate, soil types and agricultural practices of the country doing the assessment. Because ecological and environmental studies must be representative of national conditions to adequately support national risk assessments, harmonization of data requirements for these types of studies can be difficult. Harmonization can require extensive dialogue between scientists to determine which data requirements can act as common requirements. Such dialogue can also include discussions of test ''conditionalities,'' that are reflected in the test notes to the tables for the proposed data requirements.

Since 1995, the United States and Canada under the NAFTA Technical Working Group on Pesticides, Harmonization of the Evaluation of Antimicrobial Pesticides Project have worked together to harmonize data requirements for antimicrobials. These harmonization activities represent two efforts. EPA coordinates with Canada's PMRA on harmonization activities for all disciplines except efficacy. For harmonization activities for efficacy requirements EPA coordinates with Health Canada's Therapeutic Product Directorate (TPD).

EPA and PMRA approach antimicrobial data requirements differently. EPA uses a tiered testing strategy, while PMRA bases its data requirements on a defined use pattern approach. EPA and PMRA's data requirements have been carefully compared. TPD and EPA recently completed a crosswalk of EPA and TPD efficacy data requirements, which is being used for planning purposes to explore future harmonization activities. The data requirements proposed in this document for antimicrobials represent U.S. national requirements but they reflect extensive consultation with Canada. The data requirements are harmonized to a high degree. The two countries plan to continue to work together to keep data requirements for all disciplines as similar as possible.

OECD has not conducted any activity specifically aimed at harmonizing data requirements for biocides. In 1997–1998, the OECD Pesticide Program conducted a survey to collect information on the existing requirements across countries. The survey served two purposes: (1) To improve OECD's understanding of how Member countries regulate biocides, and (2) to provide information that could be used to prepare the way for future efforts to increase international co-operation in biocide regulation. The survey shows great variability. At this time OECD has no plans to work toward harmonizing these data requirements, but instead has worked at harmonizing tools and methodologies in order to reduce duplication and harmonize review procedures for possible work sharing.

C. Protocol/Guideline Harmonization

Harmonization can also involve protocol/guideline development or revisions so that the studies produced can meet common data requirements.

Issues can arise because the study protocols or guidelines used to generate the studies to meet the requirements can be different. In other words, a particular data requirement might be the same from one country to the next, but the study submitted to meet the requirement can run into acceptance problems if done according to a protocol that is acceptable in one country, but not in another. There is significant commonality in protocol design for toxicology studies among various countries, but less for ecotoxicology and environmental fate studies. Information on how to satisfy data requirements is specified in § 158.70. This section provides for both the recommended use of EPA Guidelines and for the acceptability of OECD protocols with certain caveats. Section 158.80 allows for the use of data developed in foreign countries, again with certain caveats to ensure that the data will meet EPA's needs under FIFRA and FFDCA.

D. Ballast Water Treaty

Both domestically and internationally, an emerging significant use of antimicrobials is the treatment of ballast water. Ballast water provides needed stability for safe operation of marine vessels. It is the water that is pumped in and out of the ship's ballast tanks to ensure safe operation, such as compensating for the ship's weight changes due to loading and unloading of cargo. In recent years there have been significant concerns about transport of marine species from one marine environment to another, via ballast water. Ballast water treatments are intended to kill the marine species prior to discharge. When discharged into a new environment, a new species may become invasive and disrupt the native ecology.

The International Convention for The Control and Management of Ships' Ballast Water and Sediments, 2004 (also referred to as the Ballast Water Convention) was adopted by consensus at a diplomatic conference in London on February 13, 2004. The U. S. delegation was led by the Coast Guard with participation by EPA and other Federal agencies. The treaty opened for signature on June 1, 2004, and will enter into force 12 months after ratification by 30 countries representing 35% of the world's merchant shipping tonnage. Once in force, the treaty will require that ships manage their ballast water to meet discharge standards according to a schedule in the treaty. In order to meet those discharge standards, ships will need to install equipment to treat their ballast water, including disinfection. To date, ten countries representing 3.42% of the world shipping tonnage have become Parties to the treaty.

Although the United States has not signed the treaty, ballast water discharges in U.S. waters are already regulated by the Coast Guard under the Nonindigenous Aquatic Nuisance Prevention and Control Act, as amended (16 U.S.C. 4701 *et seq.*) The existing Coast Guard ballast water management regulations can be found at 33 CFR part 151, subparts C and D. At present, the Coast Guard is engaged in further rulemaking that would set a performance standard for the quality of ballast water discharged in U.S. waters and which will further foster development of ballast water treatment technologies.

The Agency has reviewed few applications for ballast water treatments, presumably because such treatments and technologies are relatively new. Therefore, for the purpose of determining data requirements EPA determined to group ballast water treatments with antifoulant paints and coatings since both have the potential for exposure to marine organisms. OECD has not developed data requirements for ballast water.

XVII. Research Involving Human Subjects

Research with human subjects which is conducted or supported by the U. S. government is subject to regulations for the protection of human subjects referred to as the Common Rule. EPA was one of many federal departments and agencies who jointly promulgated the Common Rule in 1991. EPA's codification of the Common Rule appears at 40 CFR part 26, subpart A.

On February 6, 2006, EPA published in the **Federal Register** (71 FR 6138) a final rule amending 40 CFR part 26 by adding nine new subparts. These amendments extend regulatory protection to human subjects of research involving intentional exposure and intended for submission to EPA under the pesticide laws, when the research is conducted not by the Federal government but by private parties with no support from Federal Common Rule departments or agencies. As subsequently amended effective August 22, 2006 (71 FR 36171), this rule (1) forbids both EPA and third parties who intend to submit the research to EPA to conduct new research involving intentional exposure of pregnant or nursing women or of children; (2) extends the substantive provisions of the Common Rule to third-party human research involving intentional exposure of non-pregnant adults that is intended for submission to EPA under the pesticide laws; (3) requires submission to EPA of protocols and related information about covered human research before it is initiated; (4) establishes an independent Human Studies Review Board to review both proposals for new research and reports of covered human research on which EPA proposes to rely under the pesticide laws; and (5) forbids EPA to rely, in its actions under the pesticide laws, on research involving intentional exposure of pregnant or nursing women or of children, or which otherwise fails to meet criteria for acceptance, except in narrowly defined circumstances.

The provisions of this amended rule directly affecting third-party research intended for submission to EPA are 40 CFR part 26, subparts K, L, and M. Subpart K extends the substantive provisions of the Common Rule to third-party research involving intentional exposure of non-pregnant adult subjects that is intended for submission to EPA under the pesticide laws. Subpart K also requires submission to EPA of proposals for any covered research for review by EPA staff and the Human Studies Review Board before it is initiated, and specifies the range of information required to support any such proposal. Subpart L prohibits conduct of any new third-party research intended for submission to EPA involving intentional exposure of pregnant or nursing women or of children. Subpart M specifies the range of information required to be submitted with every report of completed research with human subjects to document its ethical conduct.

Studies required under proposed 40 CFR part 158, subpart W which involve intentional exposure of human subjects are also subject to subparts K, L, and M of 40 CFR part 26. The following data requirements in proposed § 158.2260 and § 158.2270 call for studies likely to involve intentional exposure of human subjects:

- Biological monitoring studies.
- Mixer/loader or applicator exposure studies.
- Post-application exposure studies.

If any studies undertaken to address these requirements involve intentional exposure of a human subject (as defined at 40 CFR §26.1102(i)), then the study must not be initiated before submission of protocols and supporting documentation for review by EPA and the Human Studies Review Board. The requirements for protocol submissions are specified at 40 CFR 26.1125. It may be possible to design some studies responsive to the proposed data requirements for antimicrobials so that they do not meet the regulatory definition of research involving intentional exposure of a human subject. If there is any question, however, about whether a proposed study intended for submission to EPA falls within or outside this regulatory definition, consultation with EPA is recommended before initiating the study. If EPA did not review the protocol for a study involving intentional exposure of a human subject, the study if subsequently submitted to the Agency would not be acceptable under 40 CFR 26.1705.

XVIII. Alternative Testing Paradigms

As with conventional pesticide chemicals, the Agency is committed to moving towards a more efficient and refined testing/risk assessment paradigm for antimicrobial pesticide chemicals.

A. Structure Activity Relationship (SAR)

EPA must rely upon information of appropriate quality and reliability for each decision made by the Agency. In the Office of Pesticide Programs (OPP), the evaluation process for a pesticide chemical traditionally begins with the applicant's submission of a set of studies conducted with the specific pesticide chemical of interest. The use of the results of such testing (measured data) is a logical, scientifically-rigorous process that identifies the physical, chemical, and environmental fate properties of the pesticide, as well as the dose and endpoints at which an adverse effect can occur in various animal species.

Today, there is significant interest in determining alternative testing paradigms that could offer more flexibility in the design of an integrated approach in which the selection of the required studies as well as the design of the study protocols is influenced by the existing, reliable information about the chemical. EPA is committed to moving towards alternative testing paradigms that are more efficient, reduce the use of animal testing, take full advantage of advances in science, and provide a sufficient, credible amount of data for use in a risk assessment that will support a risk management decision.

EPA is charged with developing a pesticide regulatory program that is protective of human health and the environment. Other factors that also deserve consideration in the implementation of such a program are efficiency and effectiveness. 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. From the Agency's perspective an alternative testing paradigm may also allow for a stream-lined review process for chemicals of potential lower toxicity, thus freeing resources for more in-depth, complex reviews of higher toxicity chemicals.

An integrated approach would focus on using all relevant, credible information on the chemical of interest. Applicants are cautioned that such an approach will require a different type of thought process which will incorporate significantly more planning and ''data mining'' types of activities than making arrangements to conduct the required studies. However, it could also offer a flexibility that is not always present under the currently-used, guideline-driven (study-by-study) approach.

Both SAR and QSAR techniques play a critical role in an integrated approach. In the SAR process, a chemical's molecular structure is compared to that of other chemicals for which data are available. These structural similarities are then used to make predictive judgments about a chemical's physical, chemical, and biological properties. Thus, the chemical's physical, chemical, and biological properties are a function of (or directly related to) the chemical's molecular structure. Quantitative SAR is referred to as QSAR. To develop a QSAR, a selected set of measured data on a single physical, chemical, or biological property are used to derive a model (an equation) to predict the value of that property.

EPA's Office of Pollution Prevention and Toxics administers two programs, the Interagency Testing Committee (ITC) and the New Chemicals Program (NCP) under the Toxic Substances Control Act, that have been using various forms of SAR and QSAR since the late 1970s. The ITC is an independent advisory committee that screens chemicals or classes of chemicals and prioritizes them for testing. The NCP uses an expert judgment SAR process to assess human health and has developed QSAR models to evaluate physical, chemical and environmental fate properties and ecological effects.

Additionally, other agencies (both U.S. and non-U.S.) are investigating how to use these alternative techniques. OECD has devoted a significant amount of time and effort to coordinating model development and model validation for such an integrated approach. EPA has participated on these workgroups.

During the last 6 years, OPP has made increasing use of SAR as part of its regulatory decision-making process. Documents to establish tolerance exemptions, documents to support tolerance reassessment, and Reregistration Eligibility Decision Documents have incorporated the use of SAR, when appropriate. OPP recognizes the usefulness of incorporating predictive techniques into its hazard and risk assessments, and that for certain chemicals SAR assessments and QSAR modeling could potentially form a scientifically-sound basis for hazard and risk assessments used for regulatory decisions. Over time, OPP has progressed from using SAR techniques to support a dataset of guideline type studies to, for certain assessments, relying on SAR techniques as an acceptable source of information on the chemical. OPP is now considering when and how to codify in subpart A of current part 158 that information derived from SAR assessments and/or QSAR modeling could be acceptable for fulfilling a data requirement. The submitter of such information would be expected to supply a rationale describing the utility of the information and provide documentation on the scientific validity of the information. The determination that the predicted data fulfills the data requirement would be at the sole discretion of the Agency. The Agency seeks comment on the use of predictive techniques to fulfill the part 158 subpart W data requirements, and specifically on when and if the use of SAR and QSAR should be codified in part 158, subpart A. Codification in part 158, subpart A means that SAR and QSAR techniques would be applicable to conventional, biochemical and microbial, and antimicrobial pesticide chemicals. The Agency specifically seeks comment on this issue. Comments will be used in the further development of SAR and QSAR approaches for fulfilling data requirements, but will not be addressed in the final rule for antimicrobial data requirements.

Those applicants considering use of SAR and QSAR as part of a submission package to OPP should realize SAR and Quantitative SAR (QSAR) modeling results can sometimes be used instead of measured data, but modeled data cannot be preferentially substituted for well-conducted studies (measured data). If measured data are available for a particular endpoint, then the measured data should carry the greatest weight for hazard and risk assessment purposes. Applicants are cautioned that if the Agency determines that the SAR and/or QSAR do not fulfill the data requirement, then the registration may be delayed while a study (measured data) is generated according to part 158 requirements.

At this time, the Agency intends to continue its initial explorations and begin the process to shift from the current guideline-driven (study-by-study) approach to a more integrated approach in which the use of predicted data, generated using validated models, is considered along with information from open literature and studies specifically generated under part 158 data requirements. All relevant information would be considered as part of a weight-of-evidence evaluation.

The shift to an integrated approach would occur over some time. OPP has deliberately chosen to begin this shift with antimicrobial pesticide chemicals instead of conventional pesticide chemicals for two reasons: First, most conventional pesticide chemicals are deliberately created for their biological activity and many require complex risk assessments. Few conventional pesticides have non-pesticidal uses. Second, antimicrobials also have biological activity, but are more likely to have non-pesticidal uses and, in fact, may have been assessed by other regulatory agencies. The ready availability of published literature and publicly-available assessments offer a unique opportunity for the applicant to use the available information as a starting point for fulfilling data requirements, and offering the possible option, when appropriate, of SAR and QSAR for those data requirements that are not yet fulfilled by measured data.

It should be realized that just as measured data have uncertainties, predicted data also have uncertainties. Use of different models (developed using different sets of data) would necessarily have trade-offs. Therefore, QSAR models must be used with caution. Expert judgment is required to determine the appropriate model to use and if the results of the model strike the correct balance of accuracy and precision, with the potential for few false negatives or false positives.

At this time, EPA believes that for certain endpoints, especially physical/chemical and fate properties, that SAR and QSAR might be effectively utilized to fulfill these data requirements for many antimicrobial pesticide chemicals. When considering biological properties, EPA believes that SAR and QSAR can be most effectively utilized in the evaluation of chemicals that exhibit lower toxicity for human health and/or ecotoxicity parameters. This is appropriate because the risk assessment for lower toxicity chemicals can be streamlined, i.e., through use of a screening-level assessment procedure rather than multiple tiers of assessments with progressively more data requirements.

As appropriate, OPP will consider the use of SAR and/or QSAR predictive techniques as part of the hazard assessment, and eventually the dose and endpoint selection process for antimicrobial chemicals. Under a QSAR-based approach an applicant could provide the Agency with an analysis that could frame the actual data required to register the antimicrobial pesticide chemical. For some antimicrobials, applicants may have the option of characterizing certain of the active ingredient properties via predictive techniques. It is the responsibility of the applicant to provide sufficient information to conduct a risk assessment that can be used to support a risk management decision. If the applicant believes that a SAR assessment and/or QSAR model would provide scientifically credible information that would be useful to EPA, then it is the responsibility of the applicant to provide to the Agency a rationale on the appropriateness of SAR or QSAR for that particular endpoint and sufficient documentation on how the assessment and/or model is scientifically valid. Without such information OPP cannot judge the validity of the model and therefore the acceptability of the results of the model for OPP's decision-making purposes.

At this time, the use of SAR is not yet a standardized approach in OPP, and is being handled on a case-by-case basis. Therefore, OPP has not yet developed a standardized format for submission of such information. Further information on OPP's current thinking on how SAR

and QSAR modeling can be used as part of an integrated approach to hazard and risk assessment to support a regulatory decision-making process and guidance on submission formats is contained in the support document, ''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'' which is contained in the docket for this proposed rule (Ref. 43). The Agency specifically seeks comment on this support document.

B. International Life Sciences Institute and Health and Environmental Sciences Institute Approaches

In both the proposed (70 FR 12276) and final (72 FR 60934) rules for conventional pesticide chemicals, EPA discussed the relevance and importance of the ILSI/HESI project. There have been discussions on alternative testing paradigms with the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) under the Agricultural Chemical Safety Assessment (ACSA) Technical Committee, since 2001 (Ref. 14). The focus of this effort has been toxicity testing for agricultural chemicals, but the results would also be applicable to antimicrobial pesticides.

This project, with the participation of EPA scientists, represents an evolution of the current paradigm of animal (*in vivo*) toxicity testing toward a more integrated tiered testing approach for pesticide chemicals. Under this integrated approach, both the selection of studies that would be required, as well as the design of the tests themselves, could be influenced by other substantive and reliable information about the pesticide.

The goals being pursued by EPA for this next generation of toxicity testing are to:

- Incorporate advances in science and technology in an expeditious manner.
- Identify cost effective and scientifically sound alternatives to current animal tests.
- Define a transparent, step wise plan that leads to an evolution, not revolution, in testing and assessment.
- Define a clear and credible process, with external peer-review and stakeholder participation.

All available information would be considered: Not only toxicity and dose-response data from other guideline or non-guideline studies, but also structure-activity relationships, data on the mechanism or mode of action of the chemical, pharmacokinetic data, studies that examine age-related sensitivity or susceptibility to chemical exposure, and information on potential or actual exposure to humans. These data could be used to inform a more targeted testing approach in the design of studies, or to support a position that the requirement for specific toxicology tests should be waived (i.e., the studies are not needed)or fulfilled via a means other than data generation, such as SAR.

ACSA represents the first comprehensive effort to scientifically re-design the toxicology animal-testing framework for pesticide chemicals. A series of reports authored by HESI/ILSI were published in a special edition of the *Journal of Critical Reviews in Toxicology* in January 2006 (Refs. 1, 2, 3, and 6). These four articles summarized the initial findings and recommendations.

The ACSA proposal is consistent with EPA's direction and goals to develop a more efficient and reliable testing paradigm. The ACSA approach departs significantly from the current standardized list of hazard studies used by many national and international authorities to assess pesticides. Some studies could be eliminated while endpoint coverage might be increased in redesigned studies based on responses observed in a core set of toxicity tests. Thus, it will be essential to conduct retrospective and prospective data analyses to determine whether this new testing paradigm will meet EPA's risk assessment needs.

The first retrospective analysis has been completed for the 1–year chronic dog study. Based on this retrospective analysis, which was reviewed by the FIFRA SAP, the 1–year chronic dog study is no longer required for conventional pesticide chemicals and is not proposed as a data requirement for antimicrobial chemicals. Another retrospective analysis on the 2-generation reproductive toxicity study is underway. To this end, the Office of Pesticide Programs is currently working with EPA's National Center for Computational Toxicology to populate a Toxicological Reference Database (ToxRef) with data from the rat 2-generation reproductive study, prenatal developmental toxicity and systemic toxicity studies on hundreds of pesticides that represent different classes, modes of action, and toxicity profiles. EPA will use this relational database to determine the value of endpoints currently evaluated in risk assessment (i.e., the F_1 versus F_2 responses).

From these analyses the Agency will gain other information critical for gaining scientific consensus. Such information would be the triggers, that is, the points at which a concern is indicated and thus a higher level of testing is needed. The retrospective analyses will aid the Agency in confirming the proposed ACSA triggers or in determining new ones. Once the analysis is complete, EPA will be able to complete draft guidance on testing. EPA plans to request SAP review and public comment of the analyses and draft guidance in 2008.

Additionally, there are plans to conduct several case studies using the ACSA tiered testing proposal. It is essential to test how the ACSA scheme works in practice. From such case studies, EPA will be able to assess the feasibility of a testing laboratory's ability to perform such a complex study, and will have the opportunity to evaluate the ability of the approach and its parameters to characterize known toxicants and address risk assessment needs.

In considering regulatory changes to reflect the results of EPA's consideration of ACSA, the Agency will develop scientific position papers on the new approach and recommendations for internal and external review. Internal review includes review by the FIFRA SAP and opportunities for public comment. External peer review and acceptability by other national and international regulatory authorities are considered before implementation of any new testing paradigm and data requirements. Harmonization of data requirements with our NAFTA and OECD partners is also an important factor. International regulations currently require studies that were omitted in ACSA. If EPA had requirements that were significantly different from those of the international community, then there could be significant problems for applicants in trying to satisfy multiple and different requirements world-wide.

Thus, as these analyses and the needed peer reviews are completed, EPA will have the opportunity to determine if the new testing paradigm will meet its risk assessment needs. EPA will then be able to determine what revisions to current data requirements and testing guidelines may be appropriate.

C. Computational Toxicology

EPA's Office of Research and Development (ORD) established the National Center for Computational Toxicology (NCCT) in 2005. The NCCT is developing computational tools for interpreting data from computational chemistry, high-throughput screening

(HTS) and genomic technologies as follows:

- Computational chemistry is the integration of modern computing and information technology with information on molecular biology and chemistry to predict bioactivity profiles.
- HTS is a system to rapidly and efficiently test large batches of chemicals for bioactivity utilizing robotics and automation applied to molecular biology and assay methods.
- Genomics is the study of all the genes of a cell or tissue, and their function.

EPA's ToxCast™ Program began in 2006. The underlying hypothesis for ToxCast™ is that an organism's toxicological response is driven by interactions between chemicals and biomolecular targets. ToxCast™ also includes model development to predict the potential toxicity of environmental chemicals based on bioactivity profiles. These models will identify predictive signatures, derived from the bioassay data. This means that EPA under ToxCast™ will develop methods of prioritizing chemicals for further screening and testing to assist the Agency's programs in the management and regulation of environmental contaminants (Ref. 5).

There are three phases to the development of ToxCast™:

1. The proof-of-concept phase of ToxCast™ will examine more than 300 chemicals, with rich toxicological databases, in over 400 different HTS bioassays. Predictive signatures will be created by correlating the HTS bioassay data to the known toxicity of the 300 chemicals.

2. A signature evaluation and expansion phase will focus on testing and extending the ToxCast™ predictive signatures, through the generation of HTS data on over 1,000 additional chemicals.

3. The application phase of ToxCast™ will be expanded to include a variety of high-priority chemicals that are either regulated and/or considered for regulation by EPA and potentially thousands of environmental chemicals requiring prioritization. ToxCast™ is envisioned as delivering an affordable, science-based system for categorizing chemicals.

In 2007 the NCCT awarded nine contracts for the generation of HTS and genomics data as part of the ToxCast™ chemical prioritization research program, in order to develop the ability to predict, or forecast toxicity based on bioactivity profiling. State-of-the-art HTS and genomic approaches developed by the pharmaceutical industry provide information on the impact of chemicals on biological pathways critical for the function of systems such as the heart, lungs, brain, or reproductive organs quickly and in a cost-efficient manner. Thus, results from these bioassays will provide a comprehensive and detailed overview of the potential impact of environmental chemicals upon key cellular activities.

As the ToxCast™ database grows so will confidence in the models developed from that data, as well as the resultant predictions of toxicity and potential mechanisms of action derived from the models. This could result in changing and/or reducing the use and numbers of animals in toxicity testing. This could also result in fewer *in vivo* tests being conducted as scientists and regulators learn how to interpret and use ToxCast™ predictions to then determine the chemicals that must be tested using traditional toxicity testing. Results from the first phase of ToxCast™ are anticipated by the summer of 2008. However, significant effort will be needed as ToxCast™ transitions from proof-of-concept to a useful prioritization tool.

D. National Academy of Sciences (NAS) Report Concerning Toxicity Testing and Assessment of Environmental Agents

EPA asked NAS to undertake a comprehensive review of established and emerging toxicity-testing methods and strategies. In response to this request NAS convened the Committee on Toxicity Testing and Assessment of Environmental Agents. EPA asked the Committee to conduct their assessment in two parts. Part I is a review document, discussing current and near-term methods and strategies for collecting information for human health risk assessment. Part II is a long-range vision and strategic plan for changes to human health risk assessment paradigms.

In June 2006, NAS released Toxicity Testing for Assessment of Environmental Agents: Interim Report (Ref. 20). This report fulfills EPA's Part I request. In conducting its research NAS considered numerous documents and resources such as (1) current toxicity testing protocols and various testing strategies using these protocols, (2) impediments to the use of human data, (3) strategies that rank or screen chemical substances, and (4) human health risk assessment guidance documents. The Part I report identified four objectives that EPA should strive to meet as it works to evolve its current paradigm of toxicity testing:

- *Depth,* providing the most accurate, relevant information possible for hazard identification and dose-response assessment.
- *Breadth*, providing data on the broadest possible universe of chemicals, endpoints, and life stages.
- *Animal welfare*, causing the least animal suffering possible and using the fewest possible animals.
- *Conservation*, minimizing the expenditure of money and time on testing and regulatory review.

The report acknowledged that it was difficult to simultaneously meet all four objectives.

In 2007 NAS released its Part II report entitled ''Toxicity Testing in the 21st Century: A Vision and a Strategy'' (Ref. 21). According to NAS, toxicity testing is approaching a ''scientific pivot point.'' Today, there are advances in the biological sciences that are already impacting how toxicity testing is conducted. NAS concluded that a paradigm shift would be needed to transform the current testing system but that ''the result will be a more efficient, informative and less costly system for assessing the hazards posed by industrial chemicals and pesticides.''

E. Next Steps

EPA will undertake rule-makings on a timely basis as the science progresses and changes to the data requirements are appropriate.

XIX. Animal Welfare Concerns

The Agency understands many people's concern about the use of animals for research and data development purposes. In both the proposed rule (70 FR 12276) and in the final rule (72 FR 60934) for conventional pesticide chemicals, EPA discussed its commitment to the development and use of alternative approaches to animal testing.

Taking into consideration principles of sound science and the requirements of FIFRA to protect humans and the environment, the Agency is committed to avoiding unnecessary or duplicative animal testing. As a result, the Agency has invested significant resources to investigate more integrated testing approaches that include, *in silico*, *in vitro*, and focused *in vivo* testing. The Agency's long-term goal is to create a testing paradigm so that chemicals are tested in animals only for those endpoints most relevant to each chemical's exposure or intended use. The Agency acknowledges that substantial work remains to achieve this long-term goal, but the Agency is also working on the important short-term goal to make the existing animal testing paradigm more efficient, reliable, and

responsive to its risk assessment and management needs.

As a result of the Agency's activities to move towards a more efficient animal paradigm, EPA is proposing to eliminate the existing requirement for the 1–year chronic dog study for antimicrobial pesticide chemicals.

XX. Potential Rule-Makings of the Future for Endangered Species

EPA is charged with protecting endangered and threatened species from potential harm from pesticide use. Under the Endangered Species Act, EPA must ensure that the registered uses of pesticides will not jeopardize the continued existence of endangered or threatened species, or adversely modify habitat designated as critical by the U.S. Fish and Wildlife Service or National Marine Fisheries Service. Accordingly, in its proposed and final rules for both conventional pesticide chemicals, and biochemical and microbial pesticide chemicals, the Agency discussed the possibility of future data and information needs to develop and/or refine risk assessments for endangered and threatened species. As a result of those proposed rules, EPA received comments. For the present, EPA will consider those comments in the context of its ongoing risk assessments, including those for antimicrobials. If EPA finds that it needs to amend subpart W of part 158 to normalize endangered species data requirements, it will consider those comments and any comments submitted in response to this proposed rule in the development of a future proposed rule.

For agricultural pesticides, there is generally greater specificity relative to where a pesticide may be used. If adequate geographic delineation of the use site is possible, then overlap with the locations of an endangered or threatened species may also be possible.

However, antimicrobial pesticides are different from agricultural pesticides. The Agency expects that most antimicrobial uses with potential for environmental exposure (e.g., wood preservatives, antifoulant paints, industrial wastewater discharges, ballast water discharges) could impact geographic areas of the United States that are less well defined. For example, vessels treated with antifoulant paints can occur in freshwater, estuarine, or marine areas within the U.S. (such as lakes and rivers) and in coastal waters. Wood preservatives could be used in locations that may result in an impact to terrestrial and/or aquatic organisms depending on the use of the wood, which could occur throughout the United States. Antimicrobial use sites will be much more difficult to delineate, and overlay with endangered or threatened species locations.

The Agency seeks comment on:

1. The types of data that could be useful for conducting the assessment required.

2. Projections of how long it would take to generate the needed data.

3. Whether antimicrobial use sites can be adequately correlated with endangered species locations, and suggested methods for doing so.

XXI. References

1. Barton, A, Pastoor, TP, Baetcke, K, Chambers, JE, Diliberto, J, Doerrer, NG, Driver, JH, Hastings, CE, Iyengar, S, Krieger, R, Stahl, B, and Timchalk, C. 2006. The acquisition and application of absorption, distribution, metabolism, and excretion (ADME) data in agricultural chemical safety assessments. *Critical Reviews in Toxicology*. 36, 9–35.

2. Carmichael, NG, Barton, HA, Boobis, AR, Cooper, RL, Dellarco, VL, Doerrer, NG, Fenner-Crisp, PA, Doe, JE, Lamb, JC, and Pastoor, TP. 2006. Agricultural chemical safety assessment: a multi-sector approach to the modernization of human safety requirements. *Critical Reviews in Toxicology*. 36, 1–7.

3. Cooper, RL, Lamb, JC, Barlow, SM, Bentley, K, Brady, AM, Doerrer, NG, Eisenbrandt, DL, Fenner-Crisp, PA, Hines, RN, Irvine, L, Kimmel, CA, Koeter, H, Li, AA, Makris, SL, Sheets, L, Speijers, GJA, and Whitby, K. 2006. A tiered approach to life stages testing for agricultural chemical safety assessment. *Critical Reviews in Toxicology*. 36, 69–98.

4. Dearfield, KL, Auletta, AE, Cimino, MC, and Moore, MM. 1991. Consideration in the U. S. Environmental Protection Agency's Testing Approach for Mutagenicity. *Mutation Research*. 258, 259–283.

5. Dix, DJ, Houck, KA, Martin, MT, Richard, AM, Setzer, RW, Kavlock, RJ. 2007. The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals; Toxicological Sciences 95(1), 5–12 *(accessed July 2, 2008) http://toxsci.oxfordjournals.org/cgi/content/abstract/95/1/5*.

6. Doe, JE, Boobis, AR, Blacker, A, Dellarco, VL, Doerrer, NG, Franklin, C, Goodman, JI, Kronenberg, JM, Lewis, R, McConnell, EE, Mercier, T, Moretto, A, Nolan, C, Padilla, S, Phang, W, Solecki, R, Tilbury, L, van Ravenswaay, B, and Wolf, DC. 2006. A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. *Critical Reviews in Toxicology*. 36, 37–68.

7. Food and Drug Administration (FDA) (January 1993). Sanitizing Solutions: Chemistry Guidelines for Food Additive Petitions. *(accessed July 2, 2008) http://www.cfsan.fda.gov/~dms/opa-cg3a.html*.

8. FDA (April 2002a). Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Toxicology Recommendations. *(accessed July 2, 2008) http://www.cfsan.fda.gov/~dms/opa2pmnt.html*.

9. FDA (April 2002b). Guidance For Industry: Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations. Final Guidance. *(accessed July 2, 2008) http://www.cfsan.fda.gov/~dms/opa2pmnc.html*.

10. FDA (August 2006) Estimating Dietary Intake of Substances in Food *(accessed July 2, 2008) http://www.cfsan.fda.gov/~dms/opa2cg8.html*

11. FDA (December 2007) Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations. *(accessed July 2, 2008) http://www.cfsan.fda.gov/~dms/opa3pmnc.html*

12. Halden, R, and Paull, D. 2005. Co-Occurrence of Triclocarban and Triclosan in U.S. Water Resources. *Environmental Science and Toxicology*. 39: 6, 1420–1426.

13. Health Canada, Pesticide Management Regulatory Agency: Memorandum from Don Grant, Director Health Evaluation Division: Reproductive Toxicity Testing in Proposed 40 CFR 158, Subdivision W - Data Requirements for Antimicrobial Pesticides. December 1, 1997. Attachment to Memorandum: The Assessment of Reproductive Toxicity for Antimicrobial Pesticides: The Tiered Approach of USEPA and Proposals for Change; November 1997 draft.

14. International Life Sciences Institute, Health and Environmental Sciences Institute Developing strategies for agricultural chemical safety evaluation, a report from an April 22–23, 2001 workshop. (September 2001)

15. Luster *et al*. 1992. Risk Assessment in Immunotoxicology I. Sensitivity and Predictability of Immune Tests, *Fundamental and Applied Toxicology*. 18: 200–210.

16. Luster *et al*. 1993. Risk Assessment in Immunotoxicology II. Relationships Between Immune and Host Resistance Tests, *Fundamental and Applied Toxicology*. 21: 71–82.

17. McAvoy, D, Schatowitz, B, Jacob, M, Hauk, A, and Eckhoff, W. 2002. Measurement of Triclosan in

Wastewater Treatment Systems. *Environmental Toxicology and Chemistry*, 21: 7, 1323–29.

18. Marzulli, F. and Maibach, H. *Dermatotoxicology* (5th ed.). page 284.

19. National Research Council, ''Pesticides in the Diets of Infants and Children,'' National Academy Press, Washington, D.C., 1993.

20. National Research Council 2006. Executive Summary: Toxicity Testing for Assessment of Environmental Agents: Interim Report. (Note: click on download free executive summary) *(accessed July 1, 2008) http://www.nap.edu/catalog/11523.html*.

21. National Research Council 2007. Executive Summary: Toxicity Testing in the 21st Century: A Vision and a Strategy (Note: click on download free executive summary) *(accessed July 1, 2008) http://www.nap.edu/catalog/11970.html*.

22. Santa Clara Basin Watershed Management Initiative. 2006. White Paper: Environmental Emergence of Triclosan.*(accessed July 2, 2008) http://www.scbwmi.org/PDFs/WMI_Triclosan_FinalJan06.pdf*.

23. Singer, H, Muller, S. Tixiewr, C., and Pillonel, L. 2002. Triclosan: Occurrence and Fate of a Widely Used Biocide in the Environment: Field Measurements in Wastewater Treatment Plants, Surface Waters, and Lake Sediments. *Environmental Science and Toxicology*. 36: 23, 4998–5004.

24. USEPA **Federal Register** Notice. Toxicology Data Call-In for Antimicrobial Pesticides (January 7, 1987) (FRL–3136–3).

25. USEPA (March 9, 1992). Environmental Fate and Effects Division Policy Note 1–2: Waiver of the Photodegradation in Water Data Requirement Based on the Electronic Absorption Spectra of the Pesticide (Henry Jacoby).

26. USEPA (August 5, 1991). Memorandum: Revised Mutagenicity Guideline and Requirement – Explanation, from Kerry L. Dearfield, Science Analysis and Coordination Branch.

27. USEPA (September 1993). Pesticide Reregistration Rejection Rate Analysis – Environmental Fate (EPA 738–R–93–010).

28. USEPA (February 7, 1996). Pesticide Registration (PR) Notice 96–1. Tolerance Enforcement Methods — Independent Laboratory Validation by Petitioner. *(accessed July 1, 2008) http://www.epa.gov/opppmsd1/PR_Notices/pr96–1.html*.

29. USEPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) Meeting of June 1997: A Set of Scientific Issues Being Considered by the Agency to Determine Antimicrobials Issues *(accessed July 1, 2008) http://www.epa.gov/scipoly/sap/meetings/1997/june/antimicr.htm*.

30. USEPA FIFRA SAP Meeting of December 1998: A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies (Draft 11/12/98) *(accessed July 1, 2008) http://www.epa.gov/scipoly/sap/meetings/1998/december/neuro.pdf*.

31. USEPA FIFRA SAP Report No. 99–01B: II - A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies (January 22, 1999) *(accessed July 1, 2008) http://www.epa.gov/scipoly/sap/meetings/1998/december/final2.pdf*.

32. USEPA FIFRA SAP Meeting of December 1998: Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health. (Draft—November 30, 1998). *http://www.epa.gov/scipoly/sap/meetings/1998/december/10xreq.pdf*.

33. USEPA FIFRA SAP Meeting of May 1999: Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health. (Draft—April 28, 1999). *(accessed July 1, 2008) http://www.epa.gov/scipoly/sap/meetings/1999/may/10xtx428.pdf*.

34. USEPA FIFRA SAP Meeting of April 2000: Implementation Plan for Probabilistic Ecological Assessment (August 2, 2000). *(accessed July 2, 2008) http://www.epa.gov/oscpmont/sap/meetings/2000/april/freportapril572000.pdf*.

35. USEPA (November 28, 2001). General Principles for Performing Aggregate Exposure and Risk Assessments (page 16) *(accessed July 2, 2008) http://www.epa.gov/oppfead1/trac/science/aggregate.pdf*.

36. USEPA FIFRA SAP Meeting May 2005: A Comparison of the Results of Studies on Pesticides from 12– or 24–Month Dog Studies with Dog Studies of Shorter Duration *(accessed July 2, 2008) http://www.epa.gov/scipoly/sap/meetings/2005/may2/dogstudymay05.pdf*.

37. USEPA FIFRA SAP Meeting Minutes No. 2005–03: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: A Comparison of the Results of Studies on Pesticides from 12– or 24–Month Dog Studies with Dog Studies of Shorter Duration *(accessed June 30, 2008) http://www.epa.gov/scipoly/sap/meetings/2005/may5/meetingminutesmay5_6_2005.pdf*.

38. USEPA (March 20, 2006). Length of Dog Toxicity Study(ies) that is Appropriate for Chronic RfD Determinations of Pesticide Chemicals. Health Effects Division/Office of Pesticide Programs.

39. USEPA (January 2007) FIFRA SAP Meeting Minutes *(accessed June 25, 2008) http://www.epa.gov/scipoly/sap/meetings/2007/january/january2007finalmeetingminutes.pdf*.

40. USEPA (April 2, 2007) Human Studies Review Board Meeting Minutes (EPA-HSRB–07–02) *(accessed June 25, 2008)* http://www.epa.gov/OSA/hsrb/files/April2007HSRBMtgFinalReport.pdf.

41. USEPA (February 5, 2007) Appendix B – Antimicrobial Product Use Sites and Categories Index. USEPA, Antimicrobials Division, Office of Pesticide Programs.

42. USEPA (December 31, 2007). Four Case Studies of Antimicrobial Pesticides in the Down-the-Drain Screening Model, Using the Proposed Approach for a Screening-Level Environmental Fate Assessment. USEPA, Antimicrobials Division, Office of Pesticide Programs.

43. USEPA (December 17, 2007). 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.

44. USEPA (2008). Economic Analysis of the Proposed Data Requirements for Antimicrobial Pesticides, EAB/BEAD/OPP.

45. USEPA (August 26, 2008). Supporting Statement for an Information Collection Request (ICR), Data Requirements for Antimicrobial Pesticides (Proposed Rule), EPA ICR No. 2318.01, OMB Control No. 2070–(new).

XXII. FIFRA Review Requirements

Under FIFRA section 25(a), EPA has submitted a draft of the proposed rule to the Secretary of the Department of Agriculture and the appropriate Congressional Committees. There were no comments in response to these submissions.

Under FIFRA section 21(b) EPA submitted a draft of the proposed rule to the Secretary of Health and Human Services (HHS). Their comments on this proposed rule included requests for (1) clarification on the application of these new testing requirements to current registrants, (2) information about prions, (3) the possible effects of antimicrobial residues present in food on intestinal flora, and (4) the potential for antimicrobial resistance.

EPA agrees with HHS that both current antimicrobial pesticide registrants and applicants seeking an antimicrobial registration should understand the applicability of the proposed data requirements, once

promulgated. Once effective, EPA would use the promulgated data requirements as the standard for reviewing new applications. These same promulgated data requirements, once effective, would also be used during Registration Review, when the Agency's scientists prepare the publicly available documentation on the data needed during Registration Review to complete the needed risk assessments.

EPA also agrees that the criteria for determining the efficacy of proposed anti-prion agents have not yet been established.

Concerning HHS's Center for Veterinary Medicine's (CVM) comment on intestinal flora, EPA believes that the studies proposed in this rule for use in a pesticide risk assessment are protective of human health. EPA has no specific information on effects on antimicrobial residues that would not be captured by the required health effects studies.

HHS's CVM is correct that this proposed rule does not address potential antimicrobial resistance as a result of the use of a pesticide product. While the Pesticide Program is aware of this issue, we have neither determined the extent of the problem nor how data requirements could be developed to address the issue. The Pesticide Program will continue to monitor efforts such as those of the CODEX ad hoc Intergovernmental Task Force on Antimicrobial Resistance and the Interagency Task Force on Antimicrobial Resistance, on which EPA is a participant (see *http://www.cdc.gov/drugresistance/actionplan/*). The research being conducted by the collaborating federal agencies, which is primarily focused on antibiotics, may eventually form the basis for the Pesticide Programs' approach to potential resistance as a result of the use of pesticide products. We have the authority to require studies on a case-by-case basis and to revise our data requirements in the future, if appropriate.

EPA requested that the SAP waive its review of this proposal based on the SAP's 1997 review. The SAP waived its review of this proposal on February 19, 2008.

XXIII. Statutory and Executive Order Reviews

A. Executive Order 12866

Pursuant to Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993), the Office of Management and Budget (OMB) has determined that this proposed rule is a ''significant regulatory action'' because this action might raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order. Accordingly, as a result of this OMB determination, EPA submitted this proposed rulemaking to OMB for review under Executive Order 12866. Any changes made in response to OMB comments have been documented in the public docket for this rulemaking as required by section 6(a)(3)(E) of the Executive Order.

EPA has prepared an economic analysis of the potential costs associated with this proposed action, entitled ''Economic Analysis of the Proposed Change in Data Requirements for Antimicrobial Pesticides.'' It is noted that this analysis applies only to new antimicrobial pesticides submitted for registration, and to new uses of currently registered antimicrobial pesticides. For conducting its economic analysis, EPA considered a registration action as referring to an application for registration of a new product that contains an active ingredient that is not included in any currently registered product, an application for a new product that includes the addition of a use pattern that is not currently registered for one or more active ingredients contained in the product, and an amendment of a registration of a product that includes the addition of a use pattern that is not currently registered for one or more active ingredients contained in the product.

A copy of the economic analysis (Ref. 44) can be found in the public docket for this action, and is briefly summarized here.

In the proposed rule, EPA is:

- Proposing newly codified data requirements, which are not currently established in part 161, but are routinely considered in current practice.
- Proposing changes to some of the existing data requirements such as a change from conditionally-required to required, a change in the number of test species, or expanding the number of use patterns for which the test is required.
- Proposing new data requirements, which have never been required or have rarely been required on a case-by-case basis, and have not been routinely considered during the Agency's evaluation of the data needed for the purpose of risk assessment.
- Proposing to eliminate the requirement for the chronic nonrodent study currently established in part 161.

To calculate the potential costs associated with this proposal, EPA first identified the studies that would generate the data to fulfill the proposed data requirements, and then gathered information on the price that laboratories might charge to conduct that study. To the extent possible, several cost estimates were compiled for each study. The low and high cost estimates provided by the various laboratories were averaged to account for price variations related to differences in the assumptions about the study performed (e.g., protocol, species used), and differences in the price charged by different laboratories.

EPA assumed that each data requirement would always be fulfilled and therefore data would always need to be generated for each requirement. This assumption could lead to an overestimate of the burden of the proposal, because sometimes the data are already available because the firm generated it for their own use. In such cases, the firm would simply need to submit those data to EPA, which involves less burden and cost than generating it. Some firms may have surrogate data that could be used, while others may qualify for a waiver. Some firms may share the cost of generating the data. All of these would involve lower costs than generating the data anew.

EPA then used historical data on antimicrobial pesticide registration actions that occurred from 2000 to 2005 to identify the entities that sought pesticide registration actions in the past. The data required for each registration action depends on several factors, including the type of registration action (e.g., registration of a new active ingredient food-use, registration of a new active ingredient nonfood-use, registration and amendments to registrations involving a major new use); scientific discipline (e.g., toxicology, residue chemistry, human exposure), and use pattern. The percentage of time a particular test would be required was estimated from this information. For the new data requirements, the percentage of time was estimated by EPA scientists, based on their past experience in the program and their understanding of the need for and the use of the new data requirements.

The Agency prepared an industry profile using the same historical data on pesticide registration actions to identify the companies involved in those actions, and based it on public information gathered about those companies. EPA also used this industry profile to analyze the potential impacts of the proposed rule on small businesses, the results of which are summarized in Unit XXIII.B below.

Overall the potential impact of this proposal on businesses is small, and

therefore the Agency believes that a negative effect on the availability of antimicrobial pesticide products to users is unlikely. On balance, the Agency believes that the costs of the proposed rule are justified by the benefits from enhanced protection of human health and the environment.

TABLE 2.—TOTAL ANTIMICROBIAL INDUSTRY COST PER YEAR

	Total Industry Cost per Year ($1000)
Baseline (BL)	11,080
Current Practices (CP)	11,726
Proposed Rule (PR)	14,961
Incremental Costs (PR – BL)	3,882
Newly Imposed Costs (PR-CP)	3,236

Thus, the difference between the baseline (the existing data requirements that were codified in 1984) and the Agency's current practices in requiring data is $646,000 annually. The difference between the proposed data requirements and current practices is $3.2 million annually. The difference between the proposed data requirements and the existing data requirements is $3.9 million annually. The average cost per registration action of a new antimicrobial active ingredient is approximately $1 million to $4.5 million. It is noted that this analysis applies only to new antimicrobial pesticides submitted for registration, and to new uses of currently registered antimicrobial pesticides.

For existing chemicals, the proposed part 158 subpart W data requirements would be relevant to the registration review program which began to replace the reregistration program in 2006 as a means of systematically reviewing existing registrations against the standards of FIFRA. Data needs identified under registration review for existing chemicals must be imposed under the Agency's Data Call-In (DCI) program.

EPA has not evaluated the potential burden of the proposed data requirements on registrants of existing chemicals in this proposal. However, EPA anticipates that there will be additional costs associated with the proposed studies under Registration Review. For each chemical, EPA will evaluate the specific need for additional data, including studies proposed today. Stakeholders and the public have opportunities for input, consultation and involvement concerning individual pesticide cases throughout the registration review process. Although EPA has identified the schedule for which chemicals will be reviewed over the next few years, the evaluation of data needs has not been done. Thus, the costs are unknown. EPA will articulate the specific burden and costs associated with each DCI pursuant to the appropriate Information Collection Request (ICR) approvals under the Paperwork Reduction Act (PRA).

B. Regulatory Flexibility Act

Pursuant to section 605(b) of the Regulatory Flexibility Act (RFA), 5 USC 601 *et seq.*, the Agency hereby certifies that this action will not have a significant adverse economic impact on a substantial number of small entities. The factual basis for the Agency's determination is presented in the small entity impact analysis prepared as part of the economic analysis for this proposed rule (Ref. 44), which is summarized in Unit XXIII.A., and a copy of which is available in the docket for this rulemaking. The following is a brief summary of the factual basis for this certification.

Under the RFA, small entities include small businesses, small organizations, and small governmental jurisdictions. For purposes of assessing the impacts of today's proposed rule on small entities, small entity is defined in accordance with the RFA as: (1) a small business as defined by the Small Business Administration's (SBA) regulations at 13 CFR 121.201, which is based on either the maximum number of employees or on the sales for small businesses in each industry sector, as defined by a 6–digit NAICS code; (2) a small governmental jurisdiction that is a government of a city, county, town, school district or special district with a population of less than 50,000; and (3) a small organization that is any not-for-profit enterprise which is independently owned and operated and is not dominant in its field. EPA has determined that this rulemaking does not impact any small governmental jurisdictions or any small not-for-profit enterprise because these entities are rarely pesticide applicants or registrants.

Some of the small entities directly regulated by this rulemaking are in the pesticide and other agricultural chemical manufacturing industry sector (NAICS code 325320). Firms in this sector are considered small under the RFA definition if they employ 500 or fewer people. The economic analysis for this proposed rule specifies the NAICS code used for each of the firms analyzed.

As detailed in the Economic Analysis, EPA estimates that 750 unique parent companies constitute the total universe of pesticide antimicrobial registrants. Of these, based on the SBA definition of a small business and the available sales data for these firms, EPA estimates that 500, or approximately 67%, qualify as a small business. The available antimicrobial pesticide registration data for 2000–2005 indicates that only a small portion of the 500 registrants are likely to be impacted by the proposed regulation. Specifically, 64 firms with antimicrobial registrations would have incurred additional costs under the proposed rule. Of the 64 firms, EPA estimates that a total of 25 small pesticide registrants would have incurred additional costs under the proposed rule.

The impacts to small antimicrobial registrants are measured as the per firm incremental cost, which is the difference between the existing data requirements in part 161 (the baseline) and those proposed in this rule. The impact of the regulation is expressed as the proportion of the average annual per firm incremental costs to the average annual firm sales.

The Agency's analysis of impacts on small businesses indicates that:

- About 25 (5%) of the 500 small firms subject to the proposal are likely to experience some impact (greater than 0%).

• About 22 (4.4%) of the 500 small firms are likely to experience an economic impact of 1% or more of gross sales.

• About 14 (2.8%) of the 500 small firms are likely to experience an economic impact of 3% or more of gross sales.

Based on the Agency's small business impact analysis, the Agency does not anticipate that the additional costs to industry resulting from this proposed rule will cause a significant adverse economic impact on a substantial number of small entities because the additional costs are a small share of gross revenues for most firms and less than 5% of small firms are likely to experience some impact.

EPA is particularly interested in receiving comment from small businesses as to the benefits, costs and impacts of this rule. Any comments should be submitted to the Agency in the manner specified under **ADDRESSES**.

C. Paperwork Reduction Act

The information collection requirements contained in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 et seq. EPA has prepared a new Information Collection Request (ICR) document identified by EPA ICR No. 2318.01, a copy of which has also been placed in the docket for this proposed rule. (Ref. 45).

Under the PRA, ''burden'' is defined at 5 CFR 1320.3(b). In addition, an agency may not conduct or sponsor, and a person is not required to respond to an information collection request unless it displays a currently valid OMB control number, or is otherwise required to submit the specific information by a statute. The OMB control numbers for certain EPA regulations in 40 CFR, after appearing in the preamble of the final rule, are listed in 40 CFR part 9 and, if applicable, included with the related collection instrument (e.g., form or survey).

The information collection activities related to the submission of data to EPA in order to register, amend or retain a new or existing pesticide product or obtain a tolerance for that product are already approved by OMB under the PRA. As such, this ICR only addresses the proposed changes to the data requirements that impact the information collection activities related to antimicrobial pesticides. The procedures for submitting data to EPA under FIFRA and the FFDCA are not changed in this proposal, and are already approved by OMB as follows:

1. The data submission activities associated with the establishment of a tolerance are currently approved under OMB Control No. 2070–0024 (EPA ICR No. 0597);

2. The data submission activities associated with the application for a new or amended registration of a pesticide are currently approved under OMB Control No. 2070–0060 (EPA ICR No. 0277);

3. The data submission activities associated with the generation of data for reregistration are currently approved under OMB Control No. 2070–0107 (EPA ICR No. 1504); and

4. The data submission activities associated with the generation of data for special review or registration review are currently approved under OMB Control No. 2070–0057 (EPA ICR No. 0922).

These program activities are an integral part of the Agency pesticide program and the corresponding ICRs are regularly renewed every three years as required by the PRA. The total estimated average annual public reporting burden currently approved by OMB for these various activities range from 8 hours to approximately 3,000 hours per respondent, depending on the activity and other factors surrounding the particular pesticide product.

In the new ICR for this proposed rule, which is based on the Economic Analysis (Ref. 44), EPA estimates that the typical current annual paperwork burden for registrants per antimicrobial pesticide registration is 194 burden hours and $12,631. This represents the baseline antimicrobial pesticide registration burden and costs. When considering the potential increase in this estimated annual burden and cost resulting from the new data requirements in this proposed rule, the Agency estimated the incremental burden and cost to be 35% of the baseline burden and costs, i.e., 68 burden hours and $4,421. Assuming an annual number of 15 antimicrobial pesticide registrations, the total annual registrant paperwork burden and costs for antimicrobial pesticide registrations are estimated to be approximately 3,929 hours and $255,773.25, of which 1,019 hours and $66,150 represent burden related to new data requirements, and $158.25 represents estimated delivery costs.

Any comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, should be directed to the docket for this proposed rule, under Docket ID number EPA–HQ–OPP–2008–0110. See ADDRESSES section at the beginning of this document for where to submit comments to EPA.

You may also submit a copy of your comments on the ICR directly to OMB. Comments to OMB should be sent to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), 725 17th Street, NW, Washington, DC 20503, Attention: Desk Office for EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after October 8, 2008, a comment to OMB is best assured of having its full effect if OMB receives it by November 7, 2008.

In the final rule, the Agency will address any comments received regarding the information collection requirements contained in this proposal. In addition, after the ICR for the final rule is approved, EPA will incorporate the increased burden into the existing ICRs as appropriate.

D. Unfunded Mandates Reform Act

Under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (Public Law 104– 4), EPA has determined that this action does not contain a Federal mandate that may result in expenditures of $100 million or more for State, local, and tribal governments, in the aggregate, or the private sector in any one year. As described in this document, the incremental costs for the proposed part 158 subpart W data requirement changes for antimicrobial pesticides is estimated at nearly $3.9 million per year for the private sector, which is below the $100 million threshold. Since State, local, and tribal governments are rarely pesticide applicants, the proposed rule is not expected to significantly or uniquely affect small governments. Accordingly, this action is not subject to the requirements of sections 202 and 205 of UMRA.

E. Executive Order 13132

Pursuant to Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999), EPA has determined that this proposed rule does not have ''federalism implications,'' because it will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government, as specified in the Order. As indicated above, instances where a state is a registrant are extremely rare. Therefore, this proposed rule may seldom affect a state government. Thus, Executive Order 13132 does not apply to this proposed rule. In the spirit of the Order,

and consistent with EPA policy to promote communications between the Agency and State and local governments, EPA specifically solicits comment on this proposed rule from State and local officials.

F. Executive Order 13175

As required by Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 6, 2000), EPA has determined that this proposed rule does not have tribal implications because it will not have substantial direct effects on tribal governments, on the relationship between the Federal government and the Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes, as specified in the Order. As indicated above, at present, no tribal governments hold, or have applied for, a pesticide registration. Thus, Executive Order 13175 does not apply to this proposed rule. In the spirit of the Order, and consistent with EPA policy to promote communications between the Agency and State and local governments, EPA specifically solicits comment on this proposed rule from tribal officials.

G. Executive Order 13045

This section is not subject to Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997) because it does not propose an environmental standard that is intended to have a negatively disproportionate effect on children. To the contrary, this action will provide added protection for children from pesticide risk. The proposed data requirements are intended to address risks that, if not addressed, could have a disproportionate negative impact on children. EPA will use the data and information obtained by this proposed rule to carry out its mandate under FFDCA to give special attention to the risks of pesticides to sensitive subpopulations, especially infants and children.

H. Executive Order 12898

This proposed rule does not have an adverse impact on the environmental and health conditions in low-income and minority communities because this proposed rule only impacts entities that intend to register or currently hold a registration for an antimicrobial pesticide. Therefore, under Executive Order 12898, entitled *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (59 FR 7629, February 16, 1994), the Agency does not need to consider environmental justice-related issues.

I. National Technology Transfer and Advancement Act

Section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), 15 U.S.C. 272 note) directs EPA to use voluntary consensus standards in its regulatory activities unless to do so would be inconsistent with applicable law or impractical. Voluntary consensus standards are technical standards (e.g., materials specifications, test methods, sampling procedures, *etc.*) that are developed or adopted by voluntary consensus standards bodies. NTTAA directs EPA to provide Congress, through OMB, explanations when the Agency decides not to use available and applicable voluntary consensus standards. This regulation proposes the types of data to be required to support antimicrobial pesticide registration but does not propose to require specific methods or standards to generate those data.

This proposed regulation does not impose any technical standards that would require Agency consideration of voluntary consensus standards. The Agency invites comment on its conclusion regarding the applicability of voluntary consensus standards to this rulemaking.

J. Executive Order 12630

EPA has complied with Executive Order 12630, entitled *Governmental Actions and Interference with Constitutionally Protected Property Rights* (53 FR 8859, March 15, 1988), by examining the takings implications of this rule in accordance with the ''Attorney General's Supplemental Guidelines for the Evaluation of Risk and Avoidance of Unanticipated Takings'' issued under the Executive Order.

K. Executive Order 12988

In issuing this rule, EPA has taken the necessary steps to eliminate drafting errors and ambiguity, minimize potential litigation, and provide a clear legal standard for affected conduct, as required by section 3 of Executive Order 12988, entitled *Civil Justice Reform* (61 FR 4729, February 7, 1996).

L. Executive Order 13211

This rule is not subject to Executive Order 13211, entitled ''*Actions concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use*'' (66 FR 28355, May 22, 2001) because it is not likely to have any adverse effect on the supply, distribution, or use of energy.

Lists of Subjects in 40 CFR Part 158

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and record keeping requirements.

Lists of Subjects in 40 CFR Part 161

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and record keeping requirements.

Dated: September 24, 2008.

Stephen L. Johnson,

Administrator.

Therefore, it is proposed that 40 CFR part 158 and part 161 be amended as follows:

1. The authority citation for part 158 continues to read as follows:

Authority: 7 U.S.C. 136–136y and 21 U.S.C. 346a.

2. Section 158.1(c)(4) is revised to read as follows:

§ 158.1 Purpose and scope.

* * * * *

(c) * * *

(4) *Antimicrobial pesticides.* Subparts A, B, C, D, and W apply to antimicrobial pesticides.

3. Section 158.100 is amended by revising the heading of paragraph (a); by revising paragraph (b); by redesignating paragraph (c) as paragraph (e); and by adding new paragraphs (c) and (d) to read as follows:

§ 158.100 Pesticide use patterns.

(a). *General use patterns for conventional, biochemical, and microbial pesticides.* * * *

(b) *Pesticide use site index for conventional, biochemical, and microbial pesticides.* The Pesticide Use Site Index for Conventional, Biochemical, and Microbial Pesticides is a comprehensive list of specific pesticide use sites. The index is alphabetized separately by site for all agricultural and all nonagricultural uses. The Pesticide Use Site Index associates each pesticide use site with one or more of the 12 general use patterns. It may be used in conjunction with the data tables to determine the applicability of data requirements to specific uses. The Pesticide Use Site Index for Conventional, Biochemical, and Microbial Pesticides, which will be updated periodically, is available from

the Agency or may be obtained from the Agency's website at *http://www.epa.gov/pesticides*.

(c) *Antimicrobial pesticide use patterns.* The general use patterns for antimicrobial pesticides are described in § 158.2201.

(d) *Pesticide use site index for antimicrobial pesticides.* The Pesticide Use Site Index for Antimicrobial Pesticides is a comprehensive list of specific antimicrobial use sites. The index is alphabetized by antimicrobial use sites, and associates each antimicrobial use site with one or more of the antimicrobial use patterns. It may be used in conjunction with the data tables to determine the applicability of data requirements to specific uses. The Pesticide Use Site Index for Antimicrobial Pesticides, which will be updated periodically, is available from the Agency or may be obtained from the Agency's website at *http://www.epa.gov/pesticides/regulating/usesite/*.

(e) * * *

§ 158.400 [Amended]

4. The table in § 158.400(d) is amended by removing the category ''Efficacy of antimicrobial agents'' and all of the entries under that category.

5. Part 158 is amended by adding subpart W to read as follows:

Subpart W—Antimicrobial Pesticide Data Requirements

Sec

Subpart W—Antimicrobial Pesticide Data Requirements

§ 158.2200 Applicability.

Subpart W establishes data requirements for any pesticide product that is:

(a) A pesticide that is intended for use as an ''antimicrobial pesticide'' within the meaning of FIFRA section 2(mm)(1)(A), regardless of whether it also meets the criterion of FIFRA section 2(mm)(1)(B). That criterion excludes from the definition any antimicrobial product that is intended for a food-use requiring a tolerance or exemption under FFDCA section 408 or a food additive regulation under FFDCA section 409. EPA will apply this subpart to all products intended for an antimicrobial use, purpose or function; the exclusion in FIFRA section 2(mm)(1)(B) does not exclude products from the data requirements of this subpart.

(b) A product that bears both antimicrobial and non-antimicrobial uses or claims is subject to the data requirements for pesticides in subparts C – O, and U or V of this part with respect to its non-antimicrobial uses and claims, and to the requirements of this subpart W with respect to its antimicrobial uses and claims.

(c) A wood preservative, including a product that is intended to prevent wood degradation problems due to fungal rot or decay, sapstain, or molds.

(d) An antifoulant, including a product that is intended to kill or repel organisms that can attach to underwater surfaces, such as boat bottoms.

§ 158.2201 Antimicrobial use patterns.

(a) *Antimicrobial use patterns.* The 12 general use patterns used in the data tables in this subpart are:

(1) Agricultural premises and equipment.

(2) Food-handling/storage establishments, premises and equipment.

(3) Commercial, institutional and industrial premises and equipment.

(4) Residential and public access premises.

(5) Medical premises and equipment.

(6) Human drinking water systems.

(7) Materials preservatives.

(8) Industrial processes and water systems.

(9) Antifoulant paints and coatings.

(10) Wood preservatives.

(11) Swimming pools.

(12) Aquatic areas.

(b) *Use site index.* The Antimicrobial Use Site Index is a comprehensive list of specific antimicrobial use sites. The Index associates antimicrobial use sites with one or more of the 12 antimicrobial use patterns. It is to be used in conjunction with the data tables in this subpart to determine the applicability of data requirements to specific uses. The Antimicrobial Pesticide Use Site Index, which will be updated periodically, is available from the Agency or may be obtained from the Agency's website at *http://www.epa.gov/pesticides/regulating/usesite/*.

(c) An applicant unsure of the correct use pattern(s) for his product should consult the Agency.

§ 158.2203 Definitions.

(a) *Definitions.* The following terms are defined for the purposes of this subpart:

(1) *Disinfectant* means a substance that destroys or eliminates a specific species of infectious or other public health microorganism, but not necessarily bacterial spores, in the inanimate environment.

(2) *Fungicide* means a substance that destroys fungi (including yeasts) and fungal spores pathogenic to man or other animals in the inanimate environment.

(3) *Microbiological water purifier* means any unit, water treatment product or system that removes, kills or inactivates all types of disease-causing microorganisms from the water, including bacteria, viruses and protozoan cysts, so as to render the treated water safe for drinking.

(4) *Sanitizer* means a substance that reduces the bacterial population in the inanimate environment by significant numbers, but does not destroy or eliminate all bacteria or other microorganisms.

(5) *Sterilant* means a substance that destroys or eliminates all forms of microbial life in the inanimate environment, including all forms of vegetative bacteria, bacterial spores, fungi, fungal spores, and viruses. For purposes of this subpart, ''sporicide'' and ''sterilant'' are synonymous.

(6) *Tuberculocide* means a substance that destroys or irreversibly inactivates tubercle bacilli in the inanimate environment.

(7) *Virucide* means a substance that destroys or inactivates viruses in the inanimate environment.

(b) *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*, *Eschericha 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.

(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.

§ 158.2210 Product chemistry.

The product chemistry data requirements of subpart D of this part apply to antimicrobial products covered by this subpart.

§ 158.2220 Product performance.

(a) *General.* (1) *Product performance requirement for all antimicrobial pesticides.* Each applicant must ensure through testing that his product is efficacious when used in accordance with label directions and commonly accepted pest control practices. The Agency may require, on a case-by-case basis, submission of product performance data for any pesticide product registered or proposed for registration.

(2) *Product performance data for each product that bears a public health claim.* Each product that bears a public health claim, as described in § 158.2203(b), must be supported by product performance data, as listed in the table in this paragraph. Product performance data must be submitted with the application for registration or amended registration.

(3) *Determination of data requirements.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (c) of this section to determine the product performance data requirements for antimicrobial pesticide products.

(b) *Key.* R = Required; EP = End-use product;

(c) *Table.* The following table shows the data requirements for product performance.

TABLE — ANTIMICROBIAL PRODUCT PERFORMANCE DATA REQUIREMENTS

Guideline Number	Data Requirement	All Use Patterns	Test Substance
91–2	Products for use on hard surfaces	R	EP
91–3	Products requiring confirmatory data	R	EP
91–4	Products for use on fabrics and textiles	R	EP
91–5	Air sanitizers	R	EP
91–7	Products for control of microbial pests associated with human and animal wastes	R	EP
91–8	Products for treating water systems	R	EP

§ 158.2230 Toxicology data.

(a) *General.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (d) of this section to determine the toxicology data requirements for an antimicrobial pesticide product. Notes that apply to an individual test including specific conditions, qualifications, or exceptions are listed in paragraph (e) of this section.

(b) *Uses.* The applicant for registration must first determine whether the use is a high human exposure use or a low human exposure use. If an applicant is not sure if a specific use is a high human exposure or a low human exposure use, the applicant should consult the Agency.

(1) *High human exposure uses.* For the purpose of determining data requirements, high human exposure includes those uses which are likely to result in human exposure over a considerable portion of the human lifespan, and which are significant in terms of frequency, duration, or magnitude of exposure, i.e., uses for which there is an expectation of high, prolonged, or repeated exposure. High human exposure uses of antimicrobials 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 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.

(2) *Low human exposure nonfood and low human exposure indirect food uses.* Generally, low exposure uses are those not listed in paragraph (b)(1) of this section as high exposure uses.

(3) *Tiering of data requirements.* Applicants for registration of antimicrobials may perform tests in a tiered fashion. After the initially required tests are conducted, additional testing may be required if results of the initial tests trigger the need for additional data. Conditions that trigger the need for additional data are given in the test notes in paragraph (e) of this section.

(c) *Key.* R = Required; CR = Conditionally required; NR = Not required; MP = Manufacturing-use product; EP = End-use product; TGAI = Technical grade of the active ingredient; TEP = Typical end-use product; PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabeled; Choice = choice of several test substances depending on studies required.

(d) *Table.* The following table shows the data requirements for toxicology. The test notes appear in paragraph (e) of this section.

TABLE — ANTIMICROBIAL TOXICOLOGY DATA REQUIREMENTS

Guideline Number	Data Requirement	Use Pattern		Test Substance to Support		Test Note No.
		High Human20Exposure Uses	Low Human Exposure Uses	MP	EP	
Acute Testing						
870.1100	Acute oral toxicity - rat	R	R	MP and TGAI	EP and TGAI	1, 2
870.1200	Acute dermal toxicity	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.1300	Acute inhalation toxicity - rat	R	R	MP and TGAI	EP and TGAI	4
870.2400	Primary eye irritation - rabbit	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.2500	Primary dermal irritation	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.2600	Dermal sensitization	R	R	MP and TGAI	EP and TGAI	1, 2, 3, 5
870.6200	Acute neurotoxicity - rat	R	CR	TGAI	TGAI	6
Subchronic Testing						
870.3100	90–Day oral toxicity - rodent	R	R	TGAI	TGAI	7, 8, 9, 15
870.3150	90–Day oral toxicity - nonrodent	R	CR	TGAI	TGAI	7, 10, 11, 15
870.3250	21/28–Day dermal toxicity	CR	CR	TGAI	EP and TGAI	12, 13
870.2500	90–Day dermal toxicity	CR	CR	TGAI	EP and TGAI	7, 13, 14, 15
870.3465	90–Day inhalation - toxicity - rat	CR	CR	TGAI	TGAI	7, 15, 16, 17
870.6200	90–Day neurotoxicity - rat	R	CR	TGAI	TGAI	6, 8
Chronic Testing						
870.4100	Chronic oral toxicity - rodent	R	CR	TGAI	TGAI	18, 19, 20
870.4200	Carcinogenicity - two rodent species - rat and mouse preferred	R	CR	TGAI	TGAI	19, 21, 22
Developmental Toxicity and Reproduction						
870.3700	Prenatal developmental toxicity - rat and rabbit preferred	R	R	TGAI	TGAI	23, 24, 25, 26
870.3800	Reproduction and fertility effects	R	R	TGAI	TGAI	26, 27, 28, 29
870.6300	Developmental neurotoxicity	CR	CR	TGAI	TGAI	28, 29, 30
Mutagenicity						
870.5100	Reverse mutation assay	R	R	TGAI	TGAI	31, 32
870.5300 870.5375	*In vitro* mammalian gene mutation	R	R	TGAI	TGAI	31, 33

TABLE — ANTIMICROBIAL TOXICOLOGY DATA REQUIREMENTS—Continued

Guideline Number	Data Requirement	Use Pattern		Test Substance to Support		Test Note No.
		High Human20Exposure Uses	Low Human Exposure Uses	MP	EP	
870.5380 870.5385 870.5395	In vivo cytogenetics	R	R	TGAI	TGAI	31, 34
Special Testing						
870.7485	Metabolism and pharmacokinetics	R	CR	PAI or PAIRA	PAI or PAIRA	35
870.7200	Companion animal safety	CR	CR	NR	Choice	36
870.7600	Dermal penetration	CR	CR	Choice	Choice	37
870.7800	Immunotoxicity	R	R	TGAI	TGAI	--

(e) *Test notes.* The following test notes apply to the data requirements in the table to paragraph (d) of this section:

1. Not required if test material is a gas or highly volatile liquid.

2. For the six acute toxicity studies conducted with the end-use product, the test must be conducted using the product as formulated for sale and distribution. However, if the end-use product is labeled that the product is to be diluted for use, the applicant may also conduct certain studies using the highest diluted concentration (i.e. the least diluted product) permitted by the labeling. The end-use dilution testing is in addition to the as- formulated-for-sale testing and used only for labeling purposes. Consultation with the Agency is highly suggested to assure that the appropriate product and any appropriate dilutions are tested.

3. Not required if test material is corrosive to skin or has pH less than 2 or greater than 11.5.

4. Data are required when the product consists of, or under conditions of use will result in, a respirable material (e.g., gas, vapor, aerosol or particulates).

5. Data are required if repeated dermal exposure is likely to occur under conditions of use.

6. For low exposure uses, data are required if the neurotoxicity screen in the 90–day oral rodent study or other data indicate neurotoxicity.

7. The 90–day dermal toxicity study or 90–day inhalation toxicity study may be substituted for the 90–day oral toxicity study if the Agency determines that dermal or inhalation exposure is a major route of exposure.

8. All 90–day subchronic studies in the rodent can be designed to simultaneously fulfill the requirements of the 90–day neurotoxicity study by adding separate groups of animals for testing.

9. The 90–day study is required in the rodent for hazard characterization (possibly endpoint selection) and dose-setting for the chronic/carcinogenicity study. It is not required in the mouse, but the Agency would encourage the applicant to conduct a 90–day range finding study for the purposes of dose selection for the mouse carcinogenicity study to achieve adequate dosing and an acceptable study. The applicant is also encouraged to consult with the Agency on the results of the 90–day mouse study prior to conducting the carcinogenicity study.

10. A 1–year non-rodent study (i.e., 1–year dog study) may be required if the Agency finds that a pesticide chemical is highly bioaccumulating and is eliminated slowly. Thus it does not achieve steady state or sufficient tissue concentrations to elicit an effect during a 90–day study. EPA may require the appropriate tier II metabolism and pharmacokinetic studies to evaluate more precisely bioavailability, half life, and steady state to determine if a longer duration dog toxicity study is needed.

11. For low human exposure uses, data are required if any of the following criteria are met:

i. The use of the pesticide is likely to result in repeated human exposure over a limited portion of the human lifespan, as determined by the Agency.

ii. The use is an indirect food use (less than 200 ppb).

12. Data are required if the intended use of the antimicrobial pesticide product is expected to result in human exposure to the product, and the three following conditions are met:

i. Human exposure is via skin contact.

ii. Expected human exposure is not purposeful, and is over a limited portion of the human lifespan; however, as determined by EPA, the exposure is significant in terms of the frequency of exposure, magnitude of exposure, or the duration of exposure.

iii. Data from a subchronic 90–day dermal toxicity study are not available and the 90–day dermal toxicity study has not been triggered.

13. EP testing is required if the product or any component of the product may increase dermal absorption of the active ingredient(s) or increase toxic or pharmacologic effects, as determined by testing the TGAI or based on available information about the toxic effects of the product or its components.

14. Data are required if the use pattern is such that the dermal route would be the major route of exposure or if the active ingredient of the product is known or expected to be metabolized differently by the dermal route of exposure than by the oral route, and a metabolite of the active ingredient is the toxic moiety.

15. A 90–day oral toxicity test is not required for heating, ventilation, air conditioning, and refrigeration systems (collectively referred to as HVAC), and two 90–day toxicity tests, one by the dermal route and one by the inhalation route are required.

16. Data are required if there is the likelihood of significant repeated inhalation exposure to the pesticide as a gas, vapor, or aerosol.

17. Based on estimates of the magnitude and duration of human exposure, studies of shorter duration, e.g., 21– or 28–days, may be sufficient to satisfy this requirement. Applicants for registration may consult with the Agency to determine whether studies of shorter duration would meet this requirement.

18. Based on the positive results of the acute and/or 90–day neurotoxicity studies, or on other data indicating neurotoxicity, a chronic/neurotoxicity study (i.e. a chronic study with additional neurotoxicity evaluations) may be required to provide information about potential neurotoxic effects from long-term exposures.

19. Studies which are designed to simultaneously fulfill the requirements of both the chronic oral and carcinogenicity studies (i.e., a combined study) may be conducted.

20. For low exposure, data are required if either of the following criteria are met:

i. The use of the pesticide is likely to result in repeated human exposure over a limited portion of the human lifespan, as determined by the Agency, or

ii. The use requires that a tolerance or a tolerance exemption be established.

21. For low exposure, data are required if any of the following criteria, as determined by the Agency, are met:

i. The use of the pesticide is likely to result in significant human exposure over a considerable portion of the human life span which is significant in terms of frequency time, duration, and/or magnitude of exposure.

ii. The use requires that a tolerance or a tolerance exemption be established.

iii. The active ingredient, metabolite, degradate, or impurity

A. is structurally related to a recognized carcinogen,

B. causes mutagenic effects as demonstrated by *in vitro* or *in vivo* testing, or

C. produces a morphologic effect in any organ (e.g., hyperplasia, metaplasia) in subchronic studies that may lead to a neoplastic change.

22. If the requirement for a carcinogenicity study in any species is modified or waived for any reason, then a subchronic 90–day oral study in the same species may be required.

23. Testing in two species is required for all uses.

24. The oral route, by oral intubation, is preferred, unless the chemical or physical properties of the test substance, or the pattern of exposure, suggest a more appropriate route of exposure.

25. Additional testing by other routes of exposure may be required if the pesticide is determined to be a prenatal developmental toxicant after oral dosing.

26. The developmental toxicity study in rodents may be combined with the two-generation reproduction study in rodents by using a second mating of the parental animals in either generation. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

27. A two-generation reproduction study is required.

28. An information-based approach to testing is preferred, which utilizes the best available knowledge on the chemical (hazard, pharmacokinetic, or mechanistic data) to determine whether a standard guideline study, an enhanced guideline study, or an alternative study should be conducted to assess potential hazard to the developing animal, or in some cases to support a waiver for such testing. Applicants must submit any alternative proposed testing protocols and supporting scientific rationale to the Agency. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

29. The use of a combined two-generation reproduction/developmental neurotoxicity study that utilizes the two-generation reproduction study in rodents as a basic protocol for the addition of other endpoints or functional assessments in the immature animal is encouraged.

30. A DNT study is required using a weight-of-evidence approach when:

i. The pesticide causes treatment-related neurological effects in adult animal studies (i.e, clinical signs of neurotoxicity, neuropathology, functional or behavioral effects).

ii. The pesticide causes treatment-related neurological effects in developing animals, following pre- or post-natal exposure (i.e., nervous system malformations or neuropathy, brain weight changes in offspring, functional or behavioral changes in the offspring).

iii. The pesticide elicits a causative association between exposures and adverse neurological effects in human epidemiological studies.

iv. The pesticide evokes a mechanism that is associated with adverse effects on the development of the nervous system (i.e., structure-activity-relationship (SAR) to known neurotoxicants, altered neuroreceptor or neurotransmitter responses).

31. To enhance the weight-of-evidence determination for the pesticide's mutagenicity, the Agency requires submission of other mutagenicity test results, besides those specifically listed in this table, that may have been performed for other endpoints that may be predictive of mutagenicity. A reference list of all studies and papers known to the applicant concerning the mutagenicity of the test chemical must be submitted with the required studies.

32. Testing in *Salmonella* and *E. coli* may be acceptable, if the testing can be conducted at high enough levels, as determined by the Agency. If the testing cannot be conducted at high enough levels, then the applicant must consult with the Agency to determine other needed mutagenicity testing.

33. For the *in vitro* mammalian gene mutation study, there is a choice of assays using either mouse lymphoma L5178Y cell thymidine kinase (tk) gene locus, maximizing assay conditions for small colony expression and detection; Chinese hamster ovary (CHO) or Chinese hamster lung fibroblast (v79) cells, hypoxanthine-guanine phosphoribosyl transferase (hgprt) gene locus, accompanied by an appropriate *in vitro* test for clastogenicity; or CHO cells strains AS52, xanthine-guanine phosphoribosyl transferase (xprt) gene locus.

34. There is a choice of assays, but initial consideration should be given to the rodent bone marrow assay. The micronucleus rodent bone marrow assay is preferred; the rodent bone marrow assays using metaphase analysis (aberrations) are acceptable.

35. For low exposure, these data are required when chronic or carcinogenicity studies are also required. These data may be required if significant adverse effects are seen in available toxicology studies and these effects can be further elucidated by metabolism studies.

36. These data may be required if the product's use will result in exposure to domestic animals through, but not limited to, direct application.

37. A risk assessment assuming that dermal absorption is equal to oral absorption must be performed to determine if the dermal penetration study is required, and to identify the doses and duration of exposure for which dermal absorption is to be quantified.

§ 158.2240 Nontarget organisms.

(a) *General.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (e) of this section to determine the terrestrial and aquatic nontarget organisms and nontarget plant protection data requirements for a particular antimicrobial pesticide product. Notes that apply to an individual test including specific conditions, qualifications, or exceptions are listed in paragraph (f) of this section.

(1) Terrestrial and aquatic nontarget organism data are required to support the registration of most end-use and manufacturing-use antimicrobial products.

(2) Data are generally not required to support end-use products of a gas, highly volatile liquid, highly reactive solid, or a highly corrosive material.

(3) If the Agency determines that the transformation products of the parentcompound are more toxic, persistent, bioaccumulative, or have been shown to cause adverse effects in mammalian or aquatic reproductive studies, then data on those transformation products are required to support registration.

(4) For wood preservatives, the Agency may require data on both the parent compound, which is incorporated into wood, and on transformation/degradation products which occur in wood post-treatment or occur as dislodgeable residues (such as hand contact with treated wood) or leachate residues (such as from soil or water contact with treated wood).

(b) *Low environmental exposures.* For the purpose of determining data requirements, the low environmental exposure grouping of use patterns includes the following use patterns or partial use patterns:

(1) Agricultural premises and equipment.

(2) Food-handling/storage establishments, premises, and equipment.

(3) Commercial, institutional and industrial premises and equipment.

(4) Residential and public access premises.

(5) Medical premises and equipment.

(6) Human drinking water systems.

(7) Materials preservatives.

(8) Swimming pools.

(9) Recirculating industrial processes and water systems in which the treated water is re-used repeatedly within the system.

(c) *High environmental exposures.* For the purposes of determining data requirements, the high environmental exposure grouping of use patterns includes the following use patterns or partial use patterns:

(1) Once-through industrial processes and water systems in which the water is not re-used, and is released after a single cycle through the system.

(2) Antifoulant paints and coatings.
(3) Wood preservatives.
(4) Aquatic areas.

(d) *Key.* MP = Manufacturing use product; EP = End use product; R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of the active ingredient; TEP = Typical end-use product; PAIRA = Pure active ingredient radiolabeled; a.i. = active ingredient.

(e) *Table.* The following table shows the data requirements for nontarget organisms. The test notes appear in paragraph (f) of this section.

TABLE — ANTIMICROBIAL NONTARGET ORGANISM DATA REQUIREMENTS

Guideline Number	Data Requirement	Use Pattern					Test Substance to Support		Test Note No.
		Low Environmental Exposure	High Environmental Exposure				MP	EP	
			Industrial Processes and Water Systems(Once-Through)	Antifoulant Coatings and Paints	Wood Preservatives	Aquatic Areas			
Tier One Testing									
850.2100	Acute avian oral toxicity	R	R	R	R	R	TGAI	TGAI	1
850.1010	Acute freshwater invertebrates toxicity	R	R	R	R	R	TGAI	TGAI	2
850.1075	Acute freshwater fish toxicity	R	R	R	R	R	TGAI	TGAI	3
Higher Tier Testing									
Avian Testing									
850.2200	Avian dietary toxicity	CR	CR	CR	CR	R	TGAI	TGAI	4, 5
850.2300	Avian reproduction	CR	CR	CR	CR	R	TGAI	TGAI	1, 6
Aquatic Organisms Testing									
850.1010	Acute freshwater invertebrates toxicity	CR	R	NR	NR	R	---	TEP	2, 7
850.1075	Acute freshwater fish toxicity	CR	R	NR	NR	R	---	TEP	7
850.1025 850.1035 850.1045 850.1055 850.1075	Acute estuarine and marine organisms toxicity	CR	CR	R	CR	CR	TGAI	TGAI	8, 9
	Acute estuarine and marine organisms toxicity	CR	CR	NR	NR	CR	---	TEP	7, 8
850.1400	Fish early-life stage	CR	R	R	CR	R	TGAI	TGAI	10
850.1300 850.1350	Aquatic invertebrate life-cycle	CR	R	R	CR	R	TGAI	TGAI	10
850.1500	Fish life-cycle	CR	CR	CR	CR	CR	TGAI	TGAI	11, 12

TABLE — ANTIMICROBIAL NONTARGET ORGANISM DATA REQUIREMENTS—Continued

Guideline Number	Data Requirement	Use Pattern					Test Substance to Support		Test Note No.
		Low Environmental Exposure	High Environmental Exposure				MP	EP	
			Industrial Processes and Water Systems(Once-Through)	Antifoulant Coatings and Paints	Wood Preservatives	Aquatic Areas			
850.1710 850.1730 850.1850	Aquatic organisms, bioavailability, biomagnification, toxicity tests	CR	CR	CR	CR	CR	TGAI.PAI, degradate	TGAI.PAI, degradate	13
850.1950	Simulated or actual field testing for aquatic organisms	CR	CR	CR	CR	CR	TEP	TEP	14, 15, 16
Sediment Testing									
850.1735	Whole sediment; acute freshwater invertebrates	CR	CR	R	CR	CR	TGAI	TGAI	15, 17
850.1740	Whole sediment; acute marine invertebrates	CR	CR	R	CR	CR	TGAI	TGAI	15, 17, 19
None	Whole sediment; chronic invertebrates fresh-water and marine	CR	CR	CR	CR	CR	TGAI	TGAI	15, 18, 19
Insect Pollinator Testing									
850.3020	Honeybee acute contact	CR	NR	NR	CR	NR	TGAI	TGAI	20
850.3030	Toxicity of residues to honeybees	CR	NR	NR	CR	NR	TGAI	TEP or treated wood	21

(f) *Test notes.* The following test notes apply to the data requirements in the table to paragraph (e) of this section:

1. For low environmental exposures, data are required for one avian species. For industrial processes and water systems (once-through), antifoulant paints and coatings, wood preservatives, and aquatic areas, data are required for one waterfowl species and one upland game bird species.

2. Data are required on one freshwater aquatic invertebrate species.

3. For low environmental exposures, data are required on one species of fish, either one cold water species or a warm water species. Testing on a second species is required if the active ingredient or principal transformation products are stable in the environment and the LC_{50} in the first species is greater than 1 ppm or 1mg/L. For all other use patterns, data are required on two species of fish, one cold water species and one warm water species.

4. For low environmental exposures, industrial processes and water systems (once-through), antifoulant paints and coatings, and wood preservatives, data are required for one waterfowl species, if the avian acute oral LD_{50} (TGAI testing) is less than or equal to 100 mg a.i./kg and a.i. residues or its principal transformation products are likely to occur in avian feed items. Data on one upland game bird species are required if the avian dietary LC_{50} in the first species tested is less than or equal to 500 ppm a.i. in the diet.

5. For aquatic areas, data are required on one waterfowl species and one upland game bird species.

6. For low environmental exposures, industrial processes and water systems (once-through), antifoulant paints and coatings, and wood preservatives, data are required if one or more of the following criteria are met:

i. Birds may be subjected to repeated or continued exposure to the pesticide or any of its transformation products, especially preceding or during the breeding season.

ii. The pesticide or any of its major metabolites or degradation products are stable in the environment to the extent that a potentially toxic amount may persist in avian feed.

iii. The pesticide or any of its major metabolites or degradation products are stored or accumulated in plant or animal tissues, as indicated by the octanol/water partition coefficient (K_{ow} is greater than or equal to 1,000), accumulation studies, metabolic release and retention studies, or as indicated by structural similarity to known bioaccumulative chemicals.

iv. Any other information, such as that derived from mammalian reproduction studies that indicate that reproduction in terrestrial vertebrates may be adversely affected by the anticipated use of the pesticide product.

7. TEP testing is required for any product which meets one or more of the following conditions:

i. The estimated environmental concentration (EEC) in the aquatic environment is equal to or greater than one-half the LC_{50}/EC_{50} of the TGAI when the end-use product is used as directed.

ii. An ingredient in the end-use product other than the active ingredient is expected to enhance the toxicity of the active ingredient or to cause toxicity to aquatic organisms.

8. Data are required on one estuarine/marine mollusk, one estuarine/marine invertebrate, and one estuarine/marine fish species.

9. For low environmental exposures, industrial processes and water systems (once-through), wood preservatives, and aquatic areas, data are required if the pesticide residues from the parent compound and/or transformation products are likely to enter the estuarine/marine environment.

10. For low environmental exposures, data are required if pesticide residues from the parent compound or transformation products are likely to enter freshwater or estuarine/marine environments, as determined by the Agency. For wood preservatives, data are required if pesticide residues from the parent compound, transformation products, and/or leachates from preservative-treated wood are likely to enter freshwater or estuarine/marine environments, as determined by the Agency. Testing should be conducted with the most sensitive organism (either freshwater or estuarine/marine vertebrates, or freshwater or estuarine/marine invertebrates), as determined from the results of the acute toxicity tests (acute EC_{50} freshwater invertebrates; acute LC_{50}/EC_{50} estuarine and marine organisms; acute freshwater fish LC_{50}.)

11. Data are required on estuarine /marine species if the product is intended for direct application to the estuarine or marine environment, or the product is expected to enter this environment in significant concentrations (as determined by the Agency) because of its expected use or mobility patterns.

12. Data are required on freshwater species if the end-use product is intended to be applied directly to water, or is expected to be transported to water from the intended use site, and when one or more of the following conditions apply:

i. If the Estimated Environmental Concentration (EEC) in water is equal to or greater than 0.1 of the no-observed-effect concentration or no-observed-effect level (NOEC/NOEL) in the fish early-life stage or invertebrate life-cycle tests.

ii. If studies of other organisms indicate that the reproductive physiology of fish may be affected.

13. Not required when:

i. *The octanol/water partition coefficients of the pesticide and its major degradates are less than 1,000; or*

ii.There are no potential exposures to fish and other nontarget aquatic organisms; or

iii. The hydrolytic half-life is less than 5 days at pH 5, 7, and 9.

14. Environmental chemistry methods used to generate data associated with this study must include results of a successful confirmatory method trial by an independent laboratory. Test standards and procedures for independent laboratory validation are available as addenda to the guideline for this test requirement.

15. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

16. Data are required if the intended use pattern, and the physical/chemical properties and environmental fate characteristics of the antimicrobial indicate significant potential exposure and based on the results of the acute and chronic aquatic organism testing significant impairment of nontarget aquatic organisms could result.

17. Data are required if the half-life of the pesticide in the sediment is equal to or less than 10 days in either the aerobic soil or aquatic metabolism studies, and if one or more of the following conditions are met:

i. The soil partition coefficient (K_d) is equal to or greater than 50.

ii. The log K_{ow} is equal to or greater than 3.

iii. The K_{oc} is equal to or greater than 1,000.

18. Data are required if the EEC in sediment is > 0.1 of the acute LC_{50}/EC_{50} values and if one or more of the following conditions are met:

i. The soil partition coefficient (K_d) is equal to or greater than 50 L/kg.

ii. The log K_{ow} is equal to or greater than 3.

iii. The K_{oc} is equal to or greater than 1,000.

19. Sediment testing with estuarine/marine test species is required if the product is intended for direct application to the estuarine or marine environment or the product is expected to enter this environment in significant concentrations (as determined by the Agency) either by runoff or erosion, because of its expected use or mobility pattern.

20. Data are required only for beehive applications when the beehive (empty or occupied) is treated.

21. If beehives are constructed of treated wood a study similar to ''Honey Bee Toxicity of Residues on Foliage'' is required using treated wood instead of the foliage. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

§ 158.2250 Nontarget plant protection.

(a) *General.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (e) of this section to determine the nontarget plant protection data requirements for a particular antimicrobial pesticide product. Notes that apply to an individual test including specific conditions, qualifications, or exceptions are listed in paragraph (f) of this section.

(b) *Low environmental exposures.* For the purpose of determining data requirements, the low environmental exposure grouping of use patterns includes the following use patterns or partial use patterns:

(1) Agricultural premises and equipment.

(2) Food-handling/storage establishments, premises, and equipment.

(3) Commercial, institutional and industrial premises and equipment.

(4) Residential and public access premises.

(5) Medical premises and equipment.

(6) Human drinking water systems.

(7) Materials preservatives.

(8) Swimming pools.

(9) Recirculating industrial processes and water systems in which the treated water is re-used repeatedly within the system.

(c) *High environmental exposures.* For the purposes of determining data requirements, the high environmental exposure grouping of use patterns includes the following use patterns or partial use patterns:

(1) Once-through industrial processes and water systems in which the water is not re-used, and is released after a single cycle through the system.

(2) Antifoulant paints and coatings.

(3) Wood preservatives.

(4) Aquatic areas.

(d) *Key.* MP = Manufacturing use product; EP = End use product; R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of the active ingredient; TEP = Typical end-use product.

(e) *Table.* The following table shows the data requirements for nontarget plant protection. The test notes appear in paragraph (f) of this section.

TABLE — NONTARGET PLANT PROTECTION DATA REQUIREMENTS

Guideline Number	Data Requirement	Use Pattern					Test Substance to Support		Test Note No.
		Low Environmental Exposure	High Environmental Exposure				MP	EP	
			Industrial Processes and Water Systems(Once-Through)	Antifoulant Coatings and Paints	Wood Preservatives	Aquatic Areas			
850.4225	Seedling emergence, Tier II - dose response	CR	R	R	R	R	TEP	TEP	1, 2
850.4250	Vegetative vigor, Tier II - dose response	CR	CR	NR	R	R	TEP	TEP	1, 3
850.4400	Aquatic plant growth (aquatic vascular plant) Tier II - dose response	CR	R	R	R	R	TGAI, TEP	TGAI, TEP	2, 4
850.5400	Aquatic plant growth (algal) Tier II (dose response)	R	R	R	R	R	TGAI, TEP	TGAI, TEP	4, 5, 6
850.4300	Terrestrial field	CR	CR	CR	CR	CR	TEP	TEP	7, 8, 9
850.4450	Aquatic field	CR	CR	CR	CR	CR	TEP	TEP	7, 8, 9

(f) *Test notes.* The following test notes apply to the data requirements in the table to paragraph (e) of this section:

1. Data on only one plant species (rice, *Oryza sativa*) are required.

2. For low environmental exposures, data are required if the aquatic (algal) plant growth Tier II study demonstrates detrimental effects at less than 1.0 ppm or mg/L.

3. For low environmental exposures, and industrial processes and water systems (once-through), data are required if one or more of the following criteria are met:

i. The octanol/water partition coefficient (K_{ow}) for the active ingredient or principal transformation products ≥ 1,000 for the active ingredient or principal transformation products;

ii. The hydrolysis half-life of the active ingredient or principal transformation products in water is > 4 days.

iii. The results of the ready biodegradability study [§ 158.2280] indicate that the active ingredient or principal degradation products are not biodegradable in 28 days, i.e. the biodegradation curve has not reached a plateau for at least three determinations within the 28 days.

4. For TEP testing, data are required for the applicant's end-use product if an ingredient in the end-use product, other than the active ingredient, is expected to enhance the toxicity of the active ingredient.

5. One Tier II (dose response) study, conducted with *Selenastrum capricornutum,* is required for the low environmental exposure category grouping. If the results of this study exhibits detrimental effects (is less than 1.0 ppm or mg/L), then additional Tier II (dose response) studies are required on three species (Anabaena flos-aquae, Navicula pelliculosa, and Skeletonema costatum.

6. For industrial processes and water systems (once-through), antifoulant coatings and paints, wood preservatives, and aquatic areas, Tier II (dose response) studies are required on four species (*Anabaena flos-aquae, Navicula pelliculosa, Skeletonema costatum,* and *Selenastrum capricornutum.*

7. Environmental chemistry methods used to generate data must include the results of a successful confirmatory method trial by an independent laboratory.

8. Tests are required on a case-by-case basis based on the results of lower tier plant protection studies, adverse incident reports, intended use pattern(s), and environmental fate characteristics that indicate potential exposure.

9. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

§ 158.2260 Applicator exposure.

(a) *General.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (d) of this section to determine the applicator exposure data requirements for antimicrobial pesticide products. Notes that apply to an individual test including specific conditions, qualifications, or exceptions are listed in paragraph (e) of this section.

(1) If EPA determines that industrial standards, such as the workplace standards set by the Occupational Safety and Health Administration, provide adequate protection for a particular pesticide or a particular use pattern, applicator exposure data may not be required for that pesticide or the use pattern. Applicants should consult with the Agency on appropriate testing before the initiation of studies.

(2) The Agency may accept surrogate exposure data estimations from other sources to satisfy applicator exposure data requirements if the data meet the

basic quality assurance, quality control, good laboratory practice, and other scientific requirements set by EPA. In order to be acceptable, the Agency must find that the surrogate exposure data estimations have adequate information to address applicator exposure data requirements and contain enough adequate replicates of acceptable quality to reflect the specific use prescribed on the label and the applicator activity of concern, including formulation type, application methods and rates, type of activity, and other pertinent information. The Agency will consider using such surrogate data for evaluating human exposure on a case-by-case basis.

(3) Occupational uses include not only handlers, mixers, loaders, and applicators, but also commercial applications to residential sites. Residential uses are limited to non-occupational, i.e., non-professional, antimicrobial applications. Both occupational and residential applicator data may be required for the same product.

(b) *Criteria for testing.* Applicator exposure data described in paragraph (d) of this section are required based on toxicity and exposure criteria. Data are required if a product meets, as determined by the Agency, at least one of the toxicity criteria in paragraph (b)(1) of this section, and at least one of the exposure criteria in paragraph (b)(2) of this section.

(1) *Toxicity criteria.* i. Evidence of potentially significant adverse effects have been observed in any applicable toxicity studies.

ii. Scientifically sound epidemiological or poisoning incident data indicate that adverse health effects may have resulted from handling of the pesticide.

(2) *Exposure criteria.* i. Dermal exposure may occur during use.

ii. Respiratory exposure may occur during use.

(c) *Key.* R = Required; CR = Conditionally required; TEP = Typical end-use product.

(d) *Table.* The following table shows the data requirements for applicator exposure. The test notes appear in paragraph (e) of this section.

TABLE — ANTIMICROBIAL APPLICATOR EXPOSURE DATA REQUIREMENTS

Guideline Number	Data Requirements	Occupational	Residential	Test Substance	Test Note No
875.1100	Dermal outdoor exposure	R	R	TEP	1, 2, 3
875.1200	Dermal indoor exposure	R	R	TEP	1, 2, 3, 4
875.1300	Inhalation outdoor exposure	R	R	TEP	1, 2, 3
875.1400	Inhalation indoor exposure	R	R	TEP	1, 2, 3, 4
875.1500	Biological monitoring	CR	CR	TEP	1, 2, 3
875.1600	Data reporting and calculations	R	R	TEP	5
875.1700	Product use information	R	R	TEP	—

(e) *Test notes.* The following test notes apply to the data requirements in the table to paragraph (d) of this section:

1. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

2. Biological monitoring data may be submitted in addition to, or in lieu of, dermal and inhalation passive dosimetry exposure data, provided the human pharmacokinetics of the pesticide or metabolite/analog compounds (i.e., whichever method is selected as an indicator of body burden or internal dose) allow for the back calculation to the total internal dose.

3. For products with both indoor and outdoor uses, and similar conditions of use, data are generally required for the indoor applications only. However, data for outdoor uses are required if the Agency expects outdoor uses to result in greater exposure than indoor uses (e.g., higher use rates and application frequency, or longer exposure duration, or application methods/equipment create potential for increased dermal or inhalation exposure in outdoor versus indoor use sites). In certain cases, when a pesticide is used both indoors and outdoors under dissimilar conditions of use, the Agency may require submission of applicator exposure data for both use patterns.

4. For metal working fluids (MWFs), the Agency can provide written guidance concerning exposure, toxicity, and other data requirements for ''open'' and ''closed'' MWF systems.

5. Data reporting and calculations are required when handler exposure data are required.

§ 158.2270 Post-application exposure.

(a) *General.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (d) of this section to determine the post-application exposure data requirements for antimicrobial pesticide products. The data generated during these studies are used to determine the quantity of pesticide to which people may be exposed after application. Notes that apply to an individual test, including specific conditions, qualifications, or exceptions to the designated test, are listed in paragraph (e) of this section.

(1) For all end-use products, post-application exposure data are required when certain toxicity criteria are met and the human activities associated with the pesticide's use pattern can lead to potential adverse exposures.

(2) If EPA determines that industrial standards, such as the workplace standards set by the Occupational Safety and Health Administration, provide adequate protection for a particular pesticide or a particular use pattern, post-application exposure data may not be required for that pesticide or the use pattern. Applicants should consult with the Agency on appropriate testing before the initiation of studies.

(3) The Agency may accept surrogate exposure data estimations from other sources to satisfy applicator exposure data requirements if the data meet the basic quality assurance, quality control, good laboratory practice, and other scientific requirements set by EPA. In order to be acceptable, the Agency must find that the surrogate exposure data estimations have adequate information to address applicator exposure data requirements and contain enough adequate replicates of acceptable quality to reflect the specific use prescribed on the label and the applicator activity of concern, including formulation type, application methods and rates, type of activity, and other pertinent information. The Agency will consider using such surrogate data for evaluating human exposure on a case-by-case basis.

(b) *Criteria for Testing.* Post-application exposure data described in paragraph (d) of this section are required based on toxicity and exposure criteria. Data are required if a product meets, as determined by the Agency, at least one of the toxicity criteria in paragraph (b)(1) of this section, and at least one of the exposure criteria in paragraph (b)(2) of this section.

(1) *Toxicity criteria.* (i) Evidence of potentially significant adverse effects have been observed in any applicable toxicity studies.

(ii) Scientifically sound epidemiological or poisoning incident data indicate that adverse health effects may have resulted from handling of the pesticide.

(2) *Exposure criteria.* (i) *Outdoor uses.* (A) Occupational human post-application exposure to residues of antimicrobial pesticides could occur as the result of, but is not limited to, worker re-entry into treatment sites, clean-up and equipment maintenance tasks, handling wood preservative-treated wood, or other work-related activity.

(B) Residential human post-application exposure to residues of antimicrobial pesticides could occur following the application of antimicrobials pesticides to outdoor areas and spaces at residential sites, such as, but not limited to homes, daycare centers, and other public buildings.

(ii) *Indoor uses.* (A) Occupational human post-application exposure to pesticide residues could occur following the application of the antimicrobial pesticide to indoor spaces or surfaces.

(B) Residential human post-application exposure to pesticide residues could occur following the application of the antimicrobial pesticide to indoor spaces or surfaces at residential sites, such as, but not limited to homes, daycare centers, hospitals, schools, and other public buildings.

(c) *Key.* R = Required; CR = Conditionally required; NR = Not required; TEP = Typical end-use product.

(d) *Table.* The following table shows the data requirements for post-application exposure. The test notes appear in paragraph (e) of this section.

TABLE — ANTIMICROBIAL POST-APPLICATION EXPOSURE DATA REQUIREMENTS

Guideline Number	Data Requirement	Use Sites		Test Substance	Test Note No.
		Occupational	Residential		
875.2200	Soil residue dissipation	CR	CR	TEP	1, 2, 3
875.2300	Indoor surface residue dissipation	R	R	TEP	1, 3, 4, 5, 6
875.2400	Dermal exposure	R	R	TEP	1, 3, 7, 8
875.2500	Inhalation exposure	R	R	TEP	1, 8, 9
875.2600	Biological monitoring	CR	CR	TEP	1, 8, 10
875.2700	Product use information	R	R	TEP	---
875.2800	Description of human activity	R	R	TEP	---
875.2900	Data reporting and calculations	R	R	TEP	11
875.3000	Non-dietary ingestion exposure	NR	R	TEP	1, 12

(e) *Test notes.* The following test notes apply to the data requirements in the table to paragraph (d) of this section:

1. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

2. For residential wood preservative uses, data are required if there is likely to be soil in contact with or adjacent to treated wood, including but not limited to decks, play sets, and gazebos.

3. The applicant must submit residue dissipation data in conjunction with dermal exposure data, to establish chemical transfer coefficients used to estimate transfer of residues to human skin.

4. For wood preservatives, data are required for treated wood surfaces where post-application contact with treated wood is anticipated.

5. For occupational uses, data are required if the pesticide is applied to or around surfaces, and if the human activity data indicate that workers are likely to have post-application dermal contact with treated indoor surfaces while participating in typical activities.

6. Data are required for residential sites. This includes but is not limited to the following use patterns: commercial, institutional, and industrial premises and equipment (including residential school and daycare institutions); residential and public access premises; material preservatives (including those used in residential products including but not limited to paints and plastic toys) and wood preservatives (when contact with treated wood is likely to occur).

7. Data are required for occupational and residential use sites if the human activity data indicate the potential for post-application dermal exposures while participating in typical activities.

8. Biological monitoring data may be submitted in addition to, or in lieu of, dermal and inhalation passive dosimetry exposure data provided the human pharmacokinetics of the pesticide or metabolite/analog compounds (i.e., whichever method is selected as an indicator of body burden or internal dose) allow for a back-calculation to the total internal dose.

9. Data are required for occupational sites if the vapor pressure is greater than 1E–3 mmHg at 25° C and there is the potential for bystander exposure. Data are also required if aerosols are generated where bystanders may be exposed.

10. Biological monitoring data are required when passive dosimetry techniques are not applicable for a particular exposure scenario (such as a swimmer/spa exposure) and exposure estimates from modeling techniques used in conjunction with the toxicity data indicate a risk of concern.

11. Data reporting and calculations are required when any post-application exposure monitoring data are required.

12. Data are required for residential sites if post-application exposures, particularly those of children, are likely. The selection of a sampling method will depend on the non-dietary pathway(s) of interest. Data must be generated to consider all potential pathways of non-dietary ingestion exposure that are applicable (e.g., soil ingestion, hand-to-mouth transfer, and object-to-mouth transfer of surface residues).

§ 158.2280 Environmental fate.

(a) *General.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (e) of this section to determine the environmental fate data requirements for antimicrobial pesticide products. Notes that apply to an individual test including specific conditions, qualifications, or exceptions are listed in paragraph (f) of this section.

(1) Environmental fate data are required to support the registrations of all end-use and manufacturing-use antimicrobial products.

(2) If the Agency believes that the transformation products of the parent compound are more toxic, persistent, or bioaccumulative than the parent compound, or have been shown to cause adverse effects in mammalian or aquatic reproductive studies, then data on those transformation products are also required to support registration.

(3) For wood preservatives, the Agency may require data on both the parent compound that is incorporated into the wood, and on transformation/degradation products that occur in wood post-treatment or occur as dislodgeable residues (such as hand contact with treated wood) or leachate residues (such as from soil or water contact with treated wood).

(b) *Low environmental exposures.* For the purpose of determining data requirements, the low environmental exposure grouping of use patterns includes the following use patterns or partial use patterns:

(1) Agricultural premises and equipment.

(2) Food-handling/storage establishments, premises, and equipment.

(3) Commercial, institutional and industrial premises and equipment.

(4) Residential and public access premises.

(5) Medical premises and equipment.

(6) Human drinking water systems.

(7) Materials preservatives.

(8) Swimming pools.

(9) Recirculating industrial processes and water systems in which the treated water is re-used repeatedly within the system.

(c) *High environmental exposures.* For the purposes of determining data requirements, the high environmental exposure grouping of use patterns includes the following use patterns or partial use patterns:

(1) Once-through industrial processes and water systems in which the water is not re-used, and is released after a single cycle through the system.

(2) Antifoulant paints and coatings.

(3) Wood preservatives.

(4) Aquatic areas.

(d) *Key.* MP = Manufacturing use product; EP = End use product; R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of the active ingredient; TEP = Typical end-use product; PAIRA = Pure active ingredient radiolabeled.

(e) *Table.* The following table shows the data requirements for environmental fate. The test notes appear in paragraph (f) of this section.

TABLE—ANTIMICROBIAL ENVIRONMENTAL FATE DATA REQUIREMENTS

Guideline Number	Data Requirement	Use Pattern					Test Substance to Support		Test Note No.
		Low Environmental Exposure	High Environmental Exposure				MP	EP	
			Industrial Processes and Water Systems(Once-Through)	Antifoulant Coatings and Paints	Wood Preservatives	Aquatic Areas			
Degradation Studies - Laboratory									
835.2120	Hydrolysis	R	R	R	R	R	TGAI or PAIRA	TGAI or PAIRA	1
835.2240	Photodegradation in water	R	R	R	R	R	TGAI or PAIRA	TGAI or PAIRA	2
835.2410	Photodegradation in soil	NR	NR	NR	R	NR	TGAI or PAIRA	TGAI or PAIRA	--
Biodegradation Studies - Laboratory									
835.1110	Activated Sludge Sorption Isotherm	R	R	NR	NR	NR	TGAI	TGAI	--
835.3110	Ready Biodegradability	R	R	NR	NR	NR	TGAI	TGAI	3
850.6800	Modified Activated Sludge, Respiration Inhibition Test	R	R	NR	NR	NR	TGAI	TGAI	--
835.3220	Porous Pot Study	CR	CR	NR	NR	NR	TGAI	TGAI	4
Mobility Studies									
835.1230 835.1240	Leaching and adsorption/desorption	CR	R	R	R	R	TGAI or PAIRA	TGAI or PAIRA	5, 7
Metabolism Studies - Laboratory									

TABLE—ANTIMICROBIAL ENVIRONMENTAL FATE DATA REQUIREMENTS—Continued

Guideline Number	Data Requirement	Use Pattern					Test Substance to Support		Test Note No.
		Low Environmental Exposure	High Environmental Exposure				MP	EP	
			Industrial Processes and Water Systems(Once-Through)	Antifoulant Coatings and Paints	Wood Preservatives	Aquatic Areas			
835.4100	Aerobic soil metabolism	CR	CR	NR	R	CR	TGAI or PAIRA	TGAI or PAIRA	5, 6, 8, 9
835.4200	Anaerobic soil metabolism	CR	NR	NR	CR	NR	TGAI or PAIRA	TGAI or PAIRA	5, 8, 10
835.4300	Aerobic aquatic metabolism	CR	R	R	CR	R	TGAI or PAIRA	TGAI or PAIRA	5, 8, 10
835.4400	Anaerobic aquatic metabolism	CR	R	R	CR	R	TGAI or PAIRA	TGAI or PAIRA	5, 8, 10
Dissipation Studies -- Field									
835.6200	Aquatic (sediment)	CR	CR	CR	CR	R	TEP	TEP	5, 11, 12, 13
Ground and Surface Water Monitoring									
None	Monitoring of representative U.S. waters	CR	CR	CR	CR	CR	residue of concern	residue of concern	11, 12, 14
Special Studies									
None	Special leaching	NR	NR	R	R	NR	TGAI	TEP	15, 16

(f) *Test notes.* The following test notes apply to the data requirements in the table in paragraph (e) of this section:

1. For testing antifoulant paints and coatings, testing is to be performed with both sterile buffered distilled water and sterile synthetic seawater at pH 5, 7, and 9.

2. Not required when the electronic absorption spectra, measured at pHs 5, 7 and 9, of the chemical and its hydrolytic products, if any, show no absorption or tailing between 290 and 800 nm.

3. The selection of the particular biodegradation study depends on the physical and chemical properties of the test substance, and the results of the activated sludge sorption isotherm and the modified activated sludge studies.

4. Required if the pass criteria for the ready biodegradation study are not met. This means 70% or greater removal of dissolved organic carbon and 60% or greater of theoretical oxygen demand or theoretical carbon dioxide. These pass values must be reached in a 10–day window within the 28–day period of the test.

5. For low environmental exposure uses, data are required based on a weight-of-evidence evaluation of the results of the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests.

6. For industrial processes and water systems (once-through), data are required based on a weight-of-evidence evaluation of the results of the hydrolysis, photodegradation in water, activated sludge sorption isotherm, ready biodegradability, and modified activated sludge, respiration inhibition tests.

7. Adsorption and desorption using a batch equilibrium method is preferred. In some cases, as when the antimicrobial pesticide degrades rapidly, soil column leaching with unaged or aged columns may be more appropriate to fully characterize the potential mobility of the parent compound and major transformation products.

8. The environmental media (soil, water, hydrosoil, and biota) to be utilized in these studies must be collected from areas representative of potential use sites.

9. For industrial processes and water systems (once-through), and aquatic areas, data are required for use sites that are intermittently dry.

10. For wood preservatives, data are required if treated wood is used in aquatic environments or in soils which may become flooded or waterlogged.

11. Environmental chemistry methods used to generate data associated with this study must include results of a successful confirmatory method trial by an independent laboratory.

12. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

13. For industrial processes and water systems (once-through), antifoulant paints and coatings, and wood preservatives, data are required based on the potential for aquatic exposure and if the weight-of-evidence indicates that the active ingredient or principal transformation products are likely to have the potential for persistence, mobility, nontarget aquatic toxicity, or bioaccumulation.

14. Data are required if the weight-of-evidence indicates that the 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. The Agency takes into account other factors such as the toxicity of the chemical(s), available monitoring data and the vulnerability of the freshwater, estuarine, or marine water resources in the antimicrobial use area.

15. For wood preservatives, an aquatic leaching study is required. A soil leaching study is required if human or environmental exposures are likely to occur from leachates that contain the active ingredient or principal transformation products from wood treated with a preservative product. For these studies, the Agency accepts the following methods or their equivalents: American Wood Preservers' Association (AWPA) Method E11–97 (aquatic leaching), and AWPA Method E20–04 (soil leaching). Prior approval of studies conducted according to E11–97 is not required. All other protocols

must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

16. For antifoulant paints and coatings, a leaching study is required. The Agency accepts the following method or its equivalent: American Society for Testing and Materials (ASTM) Method D5108–90. Prior approval of studies conducted according to D5108–90 is not required. All other protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

§ 158.2290 Residue chemistry.

(a) *General.* Subpart B of this part and § 158.2201 describe how to use the table in paragraph (f) of this section to determine the residue chemistry data requirements for antimicrobial pesticide products.

(b) Residue chemistry data are required for products described in this paragraph.

(1) Each end-use product bearing label directions for food-uses that require a tolerance or tolerance exemption, including, but not limited to the following:

(i) Direct food uses such as antimicrobial products used to treat animal or poultry drinking water, for egg washing, or fruit and vegetable rinses.

(ii) Indirect food uses such 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 external surfaces of the substance or article, or for the purpose of protecting the substance or article itself.

(iii) Aquatic uses that have the potential to result in residues in potable water, or in water used for livestock and poultry drinking water, irrigation of crops, or water containing fish that may be used for human food.

(iv) Wood preservative or antifoulant products intended for treating wood that may be used for food purposes (e.g., lobster pots, fish cages, or fish farms).

(2) Each manufacturing-use product bearing directions for formulation into an end-use product bearing food-uses described in paragraph (b)(1) of this section.

(c) Except as described in paragraph (b) of this section, residue chemistry data are not required to support a tolerance exemption if dietary exposure estimates are not needed due to low toxicity of the active ingredient or theoretical (modeled) estimates of exposure are adequate to assess dietary risk.

(d) *Key.* R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of the active ingredient; TEP = Typical end-use product; PAI = Pure active ingredient; PAIRA = Pure active ingredient radiolabeled; the residue of concern is determined by the Agency.

(e) *Table.* The following table shows the data requirements for residue chemistry. The test notes appear in paragraph (f) of this section.

TABLE — ANTIMICROBIAL RESIDUE CHEMISTRY DATA REQUIREMENTS

Guideline Number	Data Requirement	Use Pattern				Test substance	Test Note No.
		Agricultural Premises	Indirect Food Uses	Direct Food Contact Uses	Aquatic Uses		
Supporting Information							
860.1100	Chemical identity	R	R	R	R	TGAI	--
860.1200	Directions for use	R	R	R	R	--	--
860.1550	Proposed tolerance	R	R	R	R	--	1
860.1560	Reasonable grounds in support of petition	R	R	R	R	--	1
860.1650	Submittal of analytical reference standards	R	R	R	R	PAI and residue of concern	2
Nature of the residue							
860.1300	Nature of the residue in plants	CR	NR	R	R	PAIRA	3, 4, 5
860.1300	Nature of the residue in livestock	R	NR	CR	CR	PAIRA or radiolabeled plant metabolite	6, 7, 8
Analytical methods							
860.1340	Residue analytical methods for enforcement of tolerances	CR	CR	R	CR	Residue of concern	9
860.1340	Residue analytical methods for data collection	CR	CR	R	CR	Residue of concern	10
860.1360	Multiresidue method testing	CR	CR	R	CR	Residue of concern	11
Magnitude of the residue							
860.1380	Storage stability	R	R	R	R	TEP or residue of concern	12

TABLE — ANTIMICROBIAL RESIDUE CHEMISTRY DATA REQUIREMENTS—Continued

Guideline Number	Data Requirement	Use Pattern				Test substance	Test Note No.
		Agricultural Premises	Indirect Food Uses	Direct Food Contact Uses	Aquatic Uses		
860.1500	Crop field trials	CR	CR	R	R	TEP	13, 14
860.1520	Processed food or feed	NR	CR	CR	CR	TEP	15
860.1480	Meat/milk/poultry/eggs	CR	CR	CR	CR	TGAI or plant metabolite	16, 17
860.1400	Potable water	R	NR	NR	R	TEP	18
860.1400	Fish	NR	NR	NR	R	TEP	19
860.1400	Irrigated crops	NR	NR	NR	CR	TEP	20
860.1460	Food-handling	NR	CR	R	NR	TEP	21
860.1540	Anticipated residues	CR	CR	CR	CR	Residue of concern	22
None	Migration studies	NR	CR	NR	NR	TGAI	23

(f) *Test notes.* The following test notes apply to the data requirements in the table to paragraph (e) of this section:

1. A petition proposing a numerical tolerance or a tolerance exemption is required for any food or feed use subject to section 408 of the FFDCA if the use is not covered by an existing tolerance or tolerance exemption.

2. An analytical reference standard is required for any food or feed use requiring a tolerance. Material safety data sheets must accompany analytical standards as specified by OSHA in 29 CFR 1910.1200.

3. For agricultural premises, data are required for postharvest storage of plant commodities.

4. Data are required for direct food contact uses, excluding egg washes, to determine the transformation products in representative foods.

5. Data are required to support applications to water if any residues could occur in irrigated crops, or to crops treated directly in the field.

6. Data are required when an antimicrobial pesticide is applied directly to livestock, to livestock premises, to livestock drinking water, to livestock feed, or to crops used for livestock feed.

7. Data are required for aquatic uses if there is the potential that the treated water could be used eventually for drinking purposes by livestock.

8. If results from the plant metabolism study show differing metabolites in plants from those found in animals, then additional livestock metabolism study(ies) involving dosing with the plant metabolite(s) may be required.

9. A residue analytical method suitable for enforcement purposes is required whenever a numeric tolerance is proposed. Enforcement methods must be supported by results of an independent laboratory validation.

10. A residue analytical method suitable for collecting data to establish tolerances must quantitate all residues of concern, as determined by the Agency.

11. Data are required to determine whether the FDA/USDA multiresidue methodology would detect and identify the antimicrobial active ingredient and its metabolites.

12. Data are required for any food or feed use requiring magnitude of the residue studies unless analytical samples are stored frozen for 30 days or less, and the active ingredient is not known to be volatile or labile.

13. Residue data are required if antimicrobial chemicals are to be applied to mushroom houses, empty or occupied beehives, wood used to construct beehives, or any use which could result in residues in food or feed.

14. If the antimicrobial chemical is applied to growing crops in the field, then the requirements of 40 CFR part 158, subpart O (terrestrial food or feed use pattern) apply.

15. Data on the nature and level of residues in processed food or feed are required if residues could potentially concentrate on processing, thus requiring the establishment of a separate tolerance higher than that of the raw agricultural commodity.

16. Data are required when the pesticide use is a direct application to livestock.

17. Data are required if livestock premises are treated or if pesticide residues are present in or on livestock feed items or intentionally added to drinking water. These studies, however, may not be required in cases where the livestock metabolism studies indicate negligible transfer of pesticide residues of concern to tissues, milk, and eggs at the maximum expected exposure level for the animals.

18. Data are required for antimicrobial pesticides applied directly to water, if there is the potential that the treated water could be used for drinking purposes by man or animals.

19. For aquatic uses, data for fish are required for antimicrobial pesticides applied directly to water inhabited, or which will be inhabited, by fish that may be caught or harvested for human consumption.

20. Data are required for antimicrobial pesticides applied directly to water that could be used for irrigation or to irrigation facilities such as ditches.

21. Data are required whenever a pesticide is to be used in a food-handling or feed handling establishment unless theoretical calculations, radiolabeled laboratory data, the nature of the residue study, or other data show that residues will not occur in food or feed. Use in a food-handling establishment also includes fresh fruits and vegetables that undergo a rinse with either a sanitizing solution, or with a disinfectant followed by a potable water rinse.

22. Data are required when estimates of risk using residues at the tolerance level may result in a risk of concern. These data may include washing, cooking, processing or degradation studies as well as market basket surveys for a more precise residue determination.

23. Migration of residue data are required for antimicrobial pesticides applied to hard food surfaces or incorporated into substrates (wood, plastic, paper, cloth, rubber or similar products) intended for contact with food or feed when theoretical (modeled) estimates of the amount of antimicrobial residue transferred to the food or feed may result in a risk of concern. Protocols must be approved by the Agency prior to the initiation of the study. Details for developing protocols are available from the Agency.

PART 161—[AMENDED]

6. The authority citation for part 161 continues to read as follows:

Authority: 7 U.S.C. 136 – 136y.

Part 161 [Removed]

7. Part 161 is removed:

[FR Doc. E8–23127 Filed 10–7–08; 8:45 am]

BILLING CODE 6560–50–S