

Slide	Narration- Mammalian Toxicology
1	Hello and welcome to the presentation on mammalian toxicology data requirements for Antimicrobial Pesticides under 158W, Data Requirements for Antimicrobial Pesticides.
2	This presentation will cover the following: toxicology data requirements under 158W; how to determine toxicology data requirements based on use pattern; important points about toxicology data requirements; toxicology data requirement examples for direct food, indirect food, and non-food uses; the importance of test notes; and alternative approaches to fulfilling the toxicology data requirements.
3	Toxicology data requirements for antimicrobial pesticides are presented in Section 158.2230 of the final rule for Part 158, subpart W. For more information, see 40 CFR section 158.2200.  The agency is required to meet the statutory standard of section 408(b)(2)(ii) of the Federal Food, Drug, and Cosmetic Act: "...that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."  Thus, toxicology data requirements are based on both the potential exposures occurring from the uses of the pesticide, including exposure duration and exposure route, as well as the need for determining the hazard of the pesticide.
4	To guide registrants in conducting studies to fulfill toxicology data requirements, the Office of Chemical Safety and Pollution Prevention (OCSPP) of EPA has established the 870 series Health Effects Test Guidelines. Studies conducted using these guidelines are intended to satisfy the data requirements for determining human health effects of pesticide chemicals under the FIFRA statute. The final 870 test guidelines can be found at the website listed on this slide.
5	This slide lists the 12 major use patterns for antimicrobial pesticides that would form the starting point for determining the toxicology data required. The use patterns shown in red lettering are patterns where it is expected that the pesticide may come into contact with food through a direct or indirect food use.
6	Specific use sites are listed within each of the 12 major use patterns.  Toxicology data requirements for the specific use sites are determined by major use pattern.  An Antimicrobial Use Site Index, or USI, has been published to assist in determining data requirements. For guidance in determining the data required, consult the USI. The USI is available in the docket and can be accessed using the web link that is shown on this slide.
7	For purposes of determining toxicology data requirements, the use patterns in the table are organized according to whether it is expected that the pesticide may come into contact with food and/or be present in water from antimicrobial uses or whether there is no expectation that the pesticide will come into contact with food and/or be present in water from antimicrobial uses.

	<p>Food use designations are reflected in the column headers in the toxicology data requirements tables. The designations, direct food use and indirect food use are applicable when there is the expectation that the pesticide may come into contact with food. The designation nonfood use is applicable when there will be no expectation that a pesticide will come into contact with food.</p> <p>Examples of direct food use, indirect food use, and non-food use data requirements are presented later to illustrate their role in determining toxicology data requirements.</p>
8	<p>To delineate further, food uses for which there is the expectation that the pesticide may come into contact with food are divided into direct and indirect food uses.</p> <p>Non –food uses, that is those uses for which there is no expectation that the pesticide may come into contact with food, are divided into two categories: specific non–food use sites and all other non-food uses.</p> <p>A chemical is considered to have a direct food use if it is intended to be applied directly to food or applied to a material or article for the purpose of treating food. Some examples include, but are not limited to, fruit and vegetable rinses and egg washing treatments.</p> <p>An indirect food use involves application of the antimicrobial pesticide in or on a material or article that comes into contact with food and may result in residues in or on food, but the use is not intended for pesticidal treatment of food. As a result of food contact with a surface, object, or material that has been treated and/or impregnated with an antimicrobial pesticide, there is a potential for residues to be present in or on food. Some examples of indirect food uses include, but are not limited to, food contact surface sanitizers, impregnated cutting boards and food packaging adhesives.</p> <p>The food use designations, direct food, indirect food, and non-food, appear in the column headers in the toxicology data requirements tables and are key considerations when determining toxicology data requirements.</p>
9	<p>It is important to note that dietary assessment contains two parts: food and drinking water. Although drinking water assessment is part of a dietary assessment, it is not part of a food assessment.</p> <p>Drinking water exposure can occur from anything that may go down-the-drain, from drinking water treatment, or from industrial discharges.</p> <p>Potential concerns for human exposure to antimicrobials from ingestion of drinking water could trigger toxicology data requirements.</p>
10	<p>The toxicology data requirements decision tree on this slide illustrates the relevance of direct food, indirect food, and non-food use designations in determining the toxicology data requirements for the food portion of a dietary assessment.</p> <p>Note that indirect food use is divided into two subcategories based on the concentration of an antimicrobial's residues in the total estimated daily dietary intake. These two subcategories</p>

	are total daily dietary intake greater than 200 ppb and total daily dietary intake less than or equal to 200 ppb. The 200 ppb level was originally used by the Food and Drug Administration, or FDA, with respect to the concentration of residues in or on food for tiering data requirements for indirect food use biocides. The Agency has also adopted the 200 ppb residue threshold for determining toxicology data requirements for the indirect food uses of antimicrobial pesticides.
11	<ul style="list-style-type: none"> <li>• To determine toxicology data requirements, the first step is to determine the major use pattern. The major use patterns for antimicrobials can be found in the USI.</li> <li>• The second step is to determine the specific use site or sites for the antimicrobial pesticide. These are listed in the USI under each major use pattern category.</li> <li>• The third step is to determine whether there is potential for exposure to the antimicrobial from direct food use, indirect food use, or nonfood use.</li> <li>• Next, consult the appropriate column of the toxicology data requirements table to determine applicable data requirements. Column descriptors include: direct food use; indirect food uses with total daily dietary intake of an antimicrobial greater than 200 parts per billion; indirect food uses with total daily dietary intake of an antimicrobial less than or equal to 200 parts per billion; nonfood uses for specified antimicrobial use patterns; and all other nonfood uses. Specified antimicrobial use patterns refer to swimming pools, aquatic areas, wood preservatives, and metal working fluids.</li> <li>• Generally, more toxicology data are required for direct food uses, indirect food uses with total daily dietary intake of an antimicrobial of greater than 200 parts per billion, and some nonfood uses for specified antimicrobial use patterns than are required for indirect food uses with daily dietary intake of antimicrobials less than or equal to 200 parts per billion and all other nonfood uses.</li> </ul>
12	<p>This slide and the next slide highlight some important points regarding toxicology data requirements.</p> <p>Note that for <u>any</u> antimicrobial use pattern, there are core toxicology data that are always required. These include:</p> <ul style="list-style-type: none"> <li>• an acute toxicity testing battery six-pack, consisting of the acute oral, acute dermal, acute inhalation, primary eye irritation, primary skin irritation, and dermal sensitization tests;</li> <li>• a mutagenicity testing battery, consisting of a reverse mutation assay, <i>in vitro</i> mammalian gene mutation assay, and <i>in vivo</i> cytogenetics assay;</li> <li>• a 90-Day toxicity study in the rat by the relevant route of exposure;</li> <li>• developmental toxicity tests in two species, preferably the rat and rabbit;</li> <li>• a reproduction and fertility effects study in the rat; and</li> <li>• an immunotoxicity study.</li> </ul> <p>The Agency has published guidance about when the acute toxicity testing battery can be waived. The link that appears on this slide provides access to this guidance.</p>

13	<ul style="list-style-type: none"> <li>Required studies are designated in the toxicology data table with an “R” for required. Required studies will always include the core data and, depending on the use site or sites, additional data would potentially be required. For example, as noted in the toxicology data requirements table, swimming pool uses, wood preservative uses, metalworking fluid uses, and aquatic area uses require toxicology data in addition to the core toxicology data.</li> <li>Again, the use pattern and specific use site or sites should be examined to determine the data required.</li> </ul>
14	<p>Other toxicology studies, in addition to the core studies and required studies, may be conditionally required. These are designated as CR in the data requirements table. The test notes that follow the toxicology data requirements tables explain the conditions under which these data are or are not required.</p> <p>For example, a study may be designated as CR based on findings from a required study. If evidence of neurotoxicity is observed in a required study, such as the subchronic oral toxicity test, a specific neurotoxicity study is triggered.</p> <p>In another example, a study may be designated as CR based on the potential to reduce laboratory animal usage, such as conduct of a combined chronic toxicity and carcinogenicity study, or addition of measurements such as Immunotoxicity to a required study to eliminate the need for two separate studies.</p>
15	<p>Note that the 158W rule contains two new toxicology data requirements. One is the developmental neurotoxicity test, which is a conditionally required study. The other is the Immunotoxicity test, which is a required study. Test notes 28, 29, and 30 provide information on the conditions under which a developmental neurotoxicity test would be required.</p>
16	<p>In the next slides, we provide three examples of how to determine toxicology -data requirements for specific antimicrobial uses.</p>
17	<p>Our first example is of a fruit and vegetable wash, which is considered to be a direct food use.</p> <ul style="list-style-type: none"> <li>By definition, a use is considered to be a direct food use if an antimicrobial pesticide is used to <b>directly treat food and/or food sources and as a result, finite residues in or on food are expected or reasonably likely to result</b>. A fruit and vegetable wash is a use that would be expected to result in finite residues of the pesticide in or on food.</li> <li>The data requirements for a direct food use of an antimicrobial pesticide are similar to those for agricultural pesticides. This is because a direct food use is interpreted the same way, whether the pesticide is an agricultural or an antimicrobial pesticide. In both cases, <b>finite residues in or on food are expected or reasonably likely to result</b>.</li> </ul> <p>In this example of a direct food use, the column header “Direct food uses” from the Toxicology Data Requirements table would be used to determine the required and conditionally required</p>

	<p>data. The next two slides from the toxicology data requirements table highlight the direct food use column and the data that are required and conditionally required.</p>
18	<p>This slide highlights the “Direct Food Uses” column and shows the acute and subchronic toxicology data required, which are designated by R for required and CR for conditionally required. For data with CR designations, consult the appropriate test notes to determine whether or not the conditions requiring these studies are met.</p>
19	<p>This slide highlights the “Direct Food Uses” column and shows the chronic, developmental toxicity and reproduction, mutagenicity, and special testing data that are required or conditionally required. For data with CR designations, consult the appropriate test notes to determine whether or not the conditions requiring these studies are met.</p> <p>Note also that there are columns that indicate the substance to be tested for both the manufacturing use product, or MP, and the end-use product, or EP. Substances to be tested include the Technical Grade Active Ingredient, or TGAI; the manufacturing use product, or MP; the end-use product, or EP; the PAI, or pure active ingredient; and the pure active ingredient, radiolabeled, or PAIRA.</p>
20	<p>The second example of how toxicology data requirements are determined is for an indirect food use. The scenario considered is a kitchen countertop treated with an antimicrobial pesticide.</p> <p>By definition, a use is considered to be an <b>indirect</b> food use if food may come into contact with an antimicrobial pesticide, <b>but the pesticide is not intended to be applied directly to food</b>. As a result of contact with a surface and/or material that has been treated and/or impregnated with an antimicrobial pesticide, there is a potential for finite residues of an antimicrobial in or on food.</p> <p>In this example, a kitchen countertop may contain an antimicrobial pesticide that is impregnated into the material. Food may come into contact with the pesticide when it is placed on the countertop and some pesticide may migrate from the countertop into the food.</p> <p>Indirect food use data requirements are based on the estimated or measured residue of the antimicrobial pesticide in the total daily dietary intake from the use and whether the residue is estimated to be greater than 200 parts per billion or less than or equal to 200 parts per billion.</p>
21	<p>For the indirect food use, consult the toxicology data requirements table to determine the data requirements under the column, “indirect food uses greater than 200 parts per billion (&gt;200ppb) or the column, “indirect food uses less than or equal to 200 parts per billion (<math>\leq</math> 200ppb), as appropriate based on estimated or measured antimicrobial residue levels.</p> <p>The toxicology data required when total daily dietary intake residue for an indirect food use is estimated or measured to be greater than 200 parts per billion will be the same as those required for a direct food use. In the majority of cases for an indirect food use, total daily dietary intake residue is expected to be less than or equal to 200 parts per billion and less data would be expected to be required.</p>

22	<p>On this slide, refer to the two columns of toxicology data required for indirect food uses. Note the difference in data requirements between these two columns. The column, “Indirect food uses less than or equal to 200 parts per billion (<math>\leq 200\text{ppb}</math>)” has fewer data requirements than the column, “Indirect food uses greater than 200 parts per billion (<math>&gt; 200 \text{ ppb}</math>)”. Note that toxicology data requirements listed in the column “Indirect food uses greater than 200 parts per billion (<math>&gt;200\text{pb}</math>)” are the same as those listed in the “Direct Food Uses” column.</p>
23	<p>Note that the toxicology data requirements for the indirect food use column, listed as “Indirect Food Uses less than or equal to 200 parts per billion (<math>\leq 200\text{ppb}</math>)”, are the same set of data as the ‘core’ toxicology data listed earlier in slide 12 of this presentation.</p>
24	<p>This third and final example explains how to determine data requirements for a nonfood use. A use is considered <b>nonfood</b> if there is <b>no reasonable expectation of finite residues in food based on the application of an antimicrobial pesticide</b>. This definition is based on the presumption that food and/or food sources will not come into contact with the antimicrobial pesticide based on the use pattern.</p> <ul style="list-style-type: none"> <li>• Use sites that fall into this category include, but are not limited to: Fuel tanks, human footwear, or nonfood areas of eating establishments, such as the area underneath a sink.</li> <li>• Specified antimicrobial use patterns which are designated as nonfood, such as swimming pools, aquatic areas, wood preservatives, and metalworking fluids, require additional toxicology data compared to those designated as “all other nonfood uses”. This difference is based on the magnitude and duration of human exposure that occurs from these specific uses.</li> <li>• Note that tolerances and/or exemptions from tolerances are not required for nonfood uses.</li> </ul>
25	<p>To determine data requirements for non-food uses, examine the column in the toxicology data requirements table titled “Non-food uses”. Nonfood uses are divided into two categories: specific nonfood uses, which are listed in the sub-column “swimming pools, aquatic areas, wood preservatives, metalworking fluids”, and “All other non-food uses”. Based on the magnitude and duration of human exposure, certain <b>specific</b> non-food uses, such as metalworking fluid uses, swimming pool uses, wood preservative uses, and aquatic areas uses, could require the same toxicology data as a direct food use.</p>
26	<p>This slide highlights the acute and subchronic data requirements for non-food uses. Note the difference in data requirements between the specified nonfood uses, “Swimming Pools, Aquatic Areas, Wood Preservatives, and Metal Working Fluids” and “All Other Nonfood Uses”. For the specified nonfood uses, more data are designated as required than for “All Other Nonfood Uses”. For data with CR designations, consult the appropriate test notes to determine whether or not the conditions requiring these data are met.</p>

27	This slide highlights the chronic, developmental and reproduction, mutagenicity, and special testing data requirements for Nonfood Uses. Again, note that more data are designated as required for the specified nonfood uses than for “All Other Nonfood Uses”.
28	<p>It is important to mention other functions of the test notes in the Toxicology Data Requirements table.</p> <ul style="list-style-type: none"> <li>• Test notes may describe studies that are required on the basis of findings from the “Core” toxicology data.</li> <li>• Test notes may also describe specific requirements for specific uses.</li> <li>• In addition, test notes may describe approaches that can result in reduction in animal usage for a specific data requirement.</li> </ul>
29	<p>An example of a test note that describes studies that are required on the basis of findings from “core” toxicology data is test note 6. Test note 6 states that a 90-day neurotoxicity study is required if evidence of neurotoxicity is observed from the neurotoxicity screen in the 90-day toxicity study for non-food uses and for indirect food uses where dietary residue is less than or equal to 200ppb.</p> <p>An example of a test note that describes specific data requirements based on a specific use is test note 15. The 90-day oral toxicity study, guideline number 870.3100, is listed as a required study for all use categories. Test note 15, however, states that a 90-day oral toxicity test is not required for HVAC systems. Instead, two 90-day studies, one by the inhalation route and one by the dermal route, are required. This is because exposure from HVAC uses is primarily by the dermal and inhalation routes of exposure. For an HVAC use, an oral study would be unnecessary since oral exposure would not be relevant.</p>
30	<p>An example of a test note that describes approaches that can result in reduction of animal usage for a data requirement is test note 8. Test note 8 states that:</p> <p>“All 90-day subchronic studies in the rodent can be designed to simultaneously fulfill the requirements of the 90-day neurotoxicity and/or immunotoxicity studies by adding separate groups of animals for testing of neurotoxicity and/or immunotoxicity parameters.”</p> <p>Prior to initiating such combined studies, protocols must be submitted to the Agency for review.</p>
31	<p>While the 158W final rule lays out the toxicology data requirements, it also discusses alternative approaches to addressing toxicology data requirements. For example:</p> <ul style="list-style-type: none"> <li>• Registrants can cite open scientific literature instead of submitting an 870 guideline study. The agency has published guidance on how we assess the acceptability and quality of open scientific literature that is cited. The first link that appears on this slide provides access to this guidance.</li> <li>• In addition, in vitro approaches can be used to address acute toxicity data requirements. For example, as an alternative to using studies on animals to determine</li> </ul>

	<p>eye irritation, OPP has published guidance that presents an acceptable alternative testing framework for using studies without animals. The second link that appears on this slide provides access to this guidance.</p> <ul style="list-style-type: none"> <li>• Data on structurally-related chemicals, including (Quantitative) Structure-Activity Relationships, also referred to as QSAR and/or SAR, can also be cited.</li> </ul>
32	<p>In using alternative approaches to fulfill toxicology data requirements, the registrant must submit all relevant information and/or data and state clearly why the approach is a valid alternative approach.</p> <ul style="list-style-type: none"> <li>• The information must be relevant to evaluating the chemicals and end-points of concern. Such information can include physical/chemical properties, environmental fate data, or biological effects.</li> <li>• The information and approach must be credible and scientifically valid.</li> <li>• The approach must be validated and the basis for the results must be transparent and reproducible. The criteria must be clear.</li> <li>• Specific details concerning the information that EPA could find useful when evaluating a SAR or QSAR are in the “NAFTA TWG Quantitative Structure Activity Relationships, or QSAR, Guidance Document” which can be accessed at the link that appears on this slide.</li> </ul>
33	<p>If you need further information or have questions on the mammalian toxicology data requirements for antimicrobial pesticides, please contact the Antimicrobials Ombudsman at</p> <p><a href="mailto:OPP_AD_Ombudsman@epa.gov">OPP_AD_Ombudsman@epa.gov</a></p> <p>This concludes the presentation on mammalian toxicology data requirements for antimicrobial pesticides.</p>