Slide	Narration- Residue Chemistry
1	Welcome to the training on 40 CFR part 158 W. This Presentation is on residue chemistry data requirements.
2	In this presentation we will start with a brief statutory framework and then introduce the dietary risk assessment approach. This will be followed by a discussion of examples of uses that result in dietary exposure. Next, we will present descriptions of direct food use, indirect food use, and nonfood use and discuss the use site index. Finally, we will discuss the 158W residue chemistry data requirements including the general provisions, the screening-level assessments, and the three residue data requirements sections: supporting information, food-contact surfaces or impregnated materials; and higher tiered.
3	It is our job at EPA to protect human health and the environment by writing and enforcing regulations based on laws passed by Congress. There are two main statutes that give the agency authority to require residue chemistry data. These statutes are the Federal Insecticide, Fungicide and Rodenticide Act, or FIFRA and the Federal Food, Drug and Cosmetic Act, or FFDCA. This schematic shows the findings we must make under each statute and the submissions we will require from registrants. Under FIFRA, the agency must prove that the pesticide will pose no unreasonable adverse risks to humans via the dietary route. We may need residue chemistry data in order to support registration and risk assessment under FIFRA. Under FFDCA, we may need to set maximum residue levels, or tolerances, for pesticides used in or on food or animal feed. In this case a petition for tolerance or exemption from tolerance will be submitted. Furthermore, under FFDCA, the agency must determine that a tolerance is safe, meaning that no harm will result from aggregate exposure to the pesticide residue. Again, residue chemistry data may be needed in order to support the aggregate assessment.
4	Since aggregate assessment was mentioned in the last slide, we would like to briefly touch on what that means. As part of the Food Quality Protection Act, or FQPA, a product is deemed “safe”, for the purposes of a safety finding, when “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide’s chemical residues, including all anticipated dietary exposure and all other exposure for which there is reliable information.”

	An Aggregate exposure assessment typically includes food, drinking water, and other non-occupational exposures. For example, someone may be exposed to the same active ingredient by food and water that they ingest, and also by dermal and inhalation exposure from painting their house. Exposure from all of these exposure routes and sources need to be combined and the combined exposure must fall below the agency's level of concern in order for a chemical to be found "safe."
5	In order to ensure that risks are below our level of concern we conduct a human health risk assessment. There are two components to risk: hazard and exposure. To identify a risk, there must be hazard and exposure, not just one or the other. For example, UV rays may pose a hazard but for someone under an umbrella there is no exposure and therefore no risk. We only conduct risk assessment if there are adverse effects associated with the active ingredient and if there is human exposure expected from the active ingredient's use pattern.
6	In order to make these findings, we rely on data information from high-end conservative exposure estimates or, if these estimates indicate potential risk concerns, we required study data. Once we have these data or estimates we use them to: Estimate acute and chronic dietary risks (which contribute to the aggregate risk), to establish a tolerance or tolerance exemption, or to determine that neither of these steps are necessary for a given chemical.
7	There are three routes of exposure that are considered in a human health risk assessment. The inhalation route, the dermal route and the oral route. In the dietary exposure assessment, we consider the oral route of exposure: exposure to pesticides in the mouth or digestive tract.
8	There are several ways that a person can be exposed to pesticides by the oral route. The most common oral exposure routes are by drinking water and ingesting food (such as a kitchen countertop use resulting in residue transfer to food items), both of which can be by indirect or direct exposure.
9	This diagram shows a few examples of uses that may result in dietary exposure. Under food exposure there are two categories, indirect and direct. Examples of antimicrobial direct food uses are fruit and vegetable rinses, fumigation, and fogging of poultry houses when animals are present. Examples of indirect food uses are food contact sanitizers,

	impregnated cutting boards or food packaging adhesives. Drinking water exposure can occur from anything that may go down the drain, for example, industrial discharges. It is important to note that the dietary assessment contains two parts: food and drinking water. Although drinking water is part of dietary assessment, it is not part of a food assessment.
10	To go into further detail, the specific description of a direct food use is as follows: As defined in the Federal Food, Drug, and Cosmetic Act at 21 U.S.C. § 201(f), a chemical is considered to have a direct food use if it is intended to be directly applied to food or applied to a material or article for the purpose of treating food. Antimicrobial use patterns that fall into this category include, but are not limited to: fruit and vegetable rinses, fogging of poultry areas when animals are present, and egg washing treatments. These types of uses are generally subject to a FFDCA clearance.
11	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 in or on food.
12	Even if a pesticide does not have directions for direct application to food or to a material or article for treatment of food, exposure to an antimicrobial pesticide may still occur resulting in residues in or on food. Use patterns that fall into this category include, but are not limited to: sanitization of dishes and utensils, food processing equipment and countertops, disinfection of food-use areas and impregnation of cutting boards, conveyor belts or food containers and/or packaging for a pesticidal purpose other than treating food. These types of food uses may be subject to a FFDCA clearance.
13	Uses that could result in dietary exposure include paper, paperboard and pulp, adhesives, coatings, plastics, polymers, cleaning products, non-laundry detergents, material preservatives, and wood products.
14	A use is generally considered to be a nonfood use when there are no resulting residues expected in or on food, for example because the antimicrobial pesticide is not expected to come into contact (directly or indirectly) with food as a result of its intended use.

	Use patterns that fall into this category include, but are not limited to: uses in fuel tanks, human footwear, or nonfood areas of eating establishments, for example, a kitchen floor cleaner. These types of uses are not subject to a FFDCA clearance.
15	This flow chart walks the registrant through likely assessment and tolerance needs for each category of direct food use, indirect food use or nonfood use. Note that the decision logic for direct and indirect food use is the same. For direct and indirect food uses, the registrant should first ask, "Are residues expected?" Let's consider an example of a use site for which the answer to the question, "Are residues expected in or on food?" is "Yes". For a fruit and vegetable wash, which is a direct food use, the registrant should submit data to support a dietary exposure assessment. In general, a tolerance or tolerance exemption would be required for this use if residues are expected so the registrants should also submit a petition. In the case in which the answer to "Are residues expected?" is "No", the registrant must provide an adequate rationale and/or demonstrate that there is no reasonable expectation of residues in or on food. Examples of an adequate rational include, but are not limited to: -Data and/or scientific rationale used to support FDA food additive or food contact notification, also referred to as FCN; -Theoretical high-end calculations or modeling demonstrating that there is no reasonable expectation of residues in or on food; -Data or scientific rationale for residue removal via a potable water rinse; -Label restrictions limiting exposure to food; -Rationale on product chemistry and/or environmental fate characteristics, such as volatility and solubility; -or residue data. If the agency determines that the registrant has provided an adequate rationale and/or demonstrated that there is no reasonable expectation of residues in or on food, then no data would be required to support a dietary assessment and no tolerance or exemption from the requirement of a tolerance is needed.

	In the case of a nonfood use, no residues would be expected in or on food for such a use. Consequently, no data would be required to support a dietary risk assessment and no tolerance or exemption from the requirement of a tolerance would be needed.
16	The descriptions and flow chart on the previous slides can be found in the Antimicrobial Use Site Index, or USI, developed by the agency to provide guidance about antimicrobial pesticide use sites and general antimicrobial pesticide use patterns. This USI guidance document is intended to assist potential registrants by helping them to identify the data that are necessary to register their products. The USI is a living document that will be updated periodically as the need arises, such as if significant new uses and technology are added to labels or if registrants request clarity on a specific aspect of the index.
17	The agency codified twelve antimicrobial use patterns in 40 CFR part 158W. These are described in the Use Site Index. The eight use patterns that have potential for exposure via food are highlighted in this slide. It is important to note that any of the 12 use patterns may have potential for exposure via drinking water.
18	This slide presents the data requirement table that appears in 40 CFR, Part 158, subpart W, Section 2290 on Residue Chemistry.
19	When interpreting the information presented in this table, it is important to consider the provisions that precede the data requirements. Note the first provision which indicates that residue chemistry data are required for antimicrobial end-use products with uses that may result in residues in or on food.
20	Another provision however, under 158.2290(c), identifies an exemption which states that "Residue chemistry data are not required under paragraph (b) of this section if no adverse effects (no toxicity endpoints) are associated with dietary exposure to the active ingredient, or If theoretical (high-end) dietary exposure estimates combined with the applicable toxicity endpoint result in acute and chronic dietary risks that are below the Agency's level of concern." This is an important provision with respect to residue chemistry data as it is likely that many products with indirect food uses will rely on the results of high-end, screening-level estimates with respect to residue chemistry data requirements.

21	The residue chemistry data requirements are broken down into three separate sections: 1. Section 1 is Supporting Information, which is addressed by test notes 1 and 2 2. Section 2 is Food-Contact Surfaces or Impregnated Materials, which is addressed by test notes 3 – 7; and 3. Section 3 is Higher Tiered data, which is addressed by test notes 8 – 18
22	The first section addresses supporting information which focuses on the general background material that is required for all applications. This includes information on chemical identity and product use, as well as tolerance/tolerance petition requirements. A petition proposing a tolerance is required under section 408 of FFDCA for food or feed uses unless the use is covered by an existing tolerance. If a tolerance or tolerance exemption is proposed, the petitioner should indicate at what levels they should be set and include any reasonable grounds in support of the petition, as appropriate. An analytical reference standard is also required if a numerical tolerance or exemption is proposed. If a use is subject to an FFDCA section 409 food additive regulation or food contact notification, the petitioner should provide that information and submit a copy of the FDA petition as well as the FDA review for the Agency's consideration.
23	The next section includes data requirements that are applicable to products with uses on food-contact surfaces or in food-contact impregnated materials. Food-contact surface uses are a very common indirect food use across many different sites including agricultural, food-handling, commercial and residential premises or equipment. As a result, the most commonly performed residue chemistry requirement will likely be the migration studies.

24	• This data requirement is composed of two study types:
	  • Residue Reduction migration study
	  • Food Transfer migration study
	• The residue reduction migration study may be a potable water rinse (PWR) study, a leaching study and/or a volatility study.

	• Nature of the residue on surfaces data may be needed if chemical fate properties not well understood. Applicants should note that if the fate properties of the active ingredient are not well understood, a nature of the residue on surfaces study may be required in order to determine the appropriate residues of concern for dietary exposure. If the nature of the residue on surfaces study is required, however, it should be conducted prior to any migration studies.
25	In general, the need for migration studies is based on whether a screening-level assessment indicates that dietary risks are above or below the Agency's level of concern. When dietary risk estimates are above the level of concern, data requirements are triggered. The Agency uses this tiered approach for Registration Review workplans and is conducting screening-level assessments to determine the acute and/or chronic dietary risks of a chemical and, as a result, the appropriate residue chemistry data requirements. This approach starts with performing the conservative Residential or Commercial Tier 1A assessment (using the residential or commercial food-contact sanitizer model) for products with food-contact surface uses in order to generate high-end, screening-level dietary risk estimates.
26	Some of the conservative exposure assumptions used in generating the Tier 1A screening-level assessments include: -that 1 mg/cm2 of product remains on the treated food-contact surface; -that all food comes into contact with a treated surface (meaning in effect, that there is 100 percent likelihood of food-to-surface contact); -and that 100 percent of the residues are transferred from the surface to the food item.
27	If the Tier 1A assessment yields dietary risks of concern, residue reduction migration study and/or Food Transfer migration study data are required. A Tier 1B assessment is then performed using the migration data to reduce the 100 percent surface-to-food transfer value, thus providing a more realistic estimate of dietary exposure and risk.
28	Antimicrobial applicants should also use this process when requesting a new, indirect food use for a product through a PRIA action. Use of the

	food-contact sanitizer models to perform a Tier 1A assessment allows applicants to determine if residue chemistry migration studies are needed (based on whether the acute and/or chronic dietary risk estimates are above the level of concern) before submitting these applications to the Agency.
29	In order for applicants to use the screening-level models to determine the dietary risk estimates for a product with food-contact surface uses, applicants must first identify the dietary points of departure or PoDs. PoDs are expressed as an acute or chronic population adjusted dose known as an aPAD or cPAD or as an acute or chronic reference dose known as an aRfD or cRfD). The dietary points of departure should be obtained from the Agency's Registration Review Final Work Plan or the most recent risk assessment for the active ingredient. Next, the dietary PoDs along with the necessary product-specific information should be entered into the residential or commercial food-contact sanitizer model, as appropriate.
30	If the resulting dietary risk estimates are **below** the Agency's level of concern, which means risk estimates that are less than 100% of the aPAD and/or cPAD using the appropriate inputs and model, then residue chemistry migration studies should not need to be generated or submitted with the new, indirect food use application. The Agency anticipates that many products will not require residue chemistry data after the screening level assessment is performed.
31	However, if the dietary risks **exceed** the Agency's level of concern (i.e., modeled risk estimates are greater than 100% of the aPAD and/or cPAD) and the fate properties of the active ingredient are well-understood, then migration data are required to allow refinement of the exposure estimates. For products expected to have reduced surface residues, a residue reduction migration study should be conducted first. It is important to note that the PWR study is appropriate only for products with potable water rinse directions on the label for the indirect food-use being assessed.

	Using the results of the residue reduction migration study, perform a Tier 1B assessment to determine if the refined risk estimates are below the level of concern. If after inclusion of the residue reduction migration study results in the Tier 1B assessment, dietary risks are **<u>below</u>** the Agency's level of concern, the residue reduction migration study should be submitted to the Agency for review with the new food-use application. No additional residue data are required at that point.
32	However, if the refined dietary risks are still above the level of concern after incorporation of these data results, or if a residue reduction migration study is not applicable to the product, a food transfer study should be generated and submitted to the Agency for review. The Agency will use the food transfer migration study results to further refine inputs into dietary exposure models. Note that testing guidance for the residue reduction and food transfer migration studies are currently under development. In the interim, applicants should submit protocols for Agency review before the initiation of testing.
33	The agency has other, similar screening-level models available to estimate dietary exposure from antimicrobial uses of adhesives, food contact paper and dish washing detergents. Applicants are encouraged to consult the *Dietary Exposure and Risk Assessment Standard Operating Procedures* document for additional details on this process.
34	This slide presents higher-tiered data requirements, most of which are applicable to direct food uses. For these types of uses screening models are not available, therefore these studies will typically need to be performed to support the uses identified. • According to test notes 8 and 9: If plants or animals can be exposed to an antimicrobial pesticide, Nature of Residue studies are required. • According to test notes 10 and 11: If a numerical tolerance is required, residue analytical methods and multi-residue methods are required. • According to test notes 12 through 18: Residue data are required if an antimicrobial pesticide can be applied to potable water, fish,

	irrigated crops, meat, milk, poultry, eggs (MMPE), food crops (also raw agricultural commodities (RACs)); can concentrate in processed food/feed; or tolerance-level dietary exposure and risk estimates exceed our level of concern.
35	For further information and questions about residue chemistry data requirements for antimicrobial pesticides, contact the Antimicrobials Division Ombudsman at: OPP_AD_Ombudsman@epa.gov This concludes our presentation on residue chemistry data requirements for antimicrobial pesticides.