

Mammalian Toxicology Data Requirements for Antimicrobial Pesticides

158W

40 CFR §158.2200



Outline

- Toxicology Data Requirements under 158W
- Determining Toxicology Data requirements based on use patterns for Antimicrobial Pesticides
- Important points about toxicology data requirements
- Toxicology data requirements examples -direct, indirect, and non-food uses
- Attributes of test notes
- Alternative approaches to fulfilling data requirements



Toxicology Data Requirements under 158W

- Toxicology data requirements for antimicrobial pesticides are presented in §158.2230 of the final rule for part 158, subpart W (See 40 CFR §158.2200).
- EPA is required to meet the statutory standard of section 408(b)(2)(ii) of the Federal Food, Drug, and Cosmetic Act (FFDCA): “...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 use(s) of the pesticide including exposure duration and exposure route, as well as the need for determining the hazard of the antimicrobial pesticide.



Toxicology Studies –OCSPP Series 870 Guidelines

- To assist registrants in conducting studies to fulfill toxicology data requirements, the Office of Chemical Safety and Pollution Prevention (OCSPP) of EPA has published the 870 series Health Effects Test Guidelines. Studies conducted using these guidelines are intended to satisfy the data requirements for determining human health impacts of pesticide chemicals under the FIFRA statute. The final 870 test guidelines can be found at:
- <http://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-870-health-effects-test-guidelines>



12 Major Use Patterns for Antimicrobial Pesticides

- 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. **Antifouling Coatings and Ballast Water Treatments**
- 10. **Wood Preservatives**
- 11. Swimming Pools and Spas
- 12. **Aquatic Areas**

*Use patterns highlighted in RED denote where potential for food contact may be expected.



Use Sites for Antimicrobial Pesticides

- Specific use sites are listed within each of the 12 major antimicrobial use patterns.
- Toxicology data requirements for specific use site(s) will be consistent with the requirements under the major use pattern that contains the specific use sites.
- A use site index has been published to assist in determining data requirements and can be consulted to help determine the toxicology data required. The index is available at www.regulations.gov under docket ID: EPA-HQ-OPP-2015-0302-0001



Determining Toxicology Data Requirements

- For purposes of determining toxicology data requirements, the use patterns in the table are organized according to:
 - whether there is the expectation 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 antimicrobial will come into contact with food and/or be present in water from antimicrobial uses
- Food use designations, direct food, indirect food, and nonfood appear in the column headers in the toxicology data tables and are key considerations when determining toxicology data requirements.



Determining Toxicology Data Requirements

- Food uses for which there is the expectation that the pesticide may come into contact with food are divided into direct food and indirect food uses
- Non-food uses, those for which there is no expectation that the pesticide may come into contact with food, are divided into specified non-food use sites and all other non-food uses
- Direct food use: Pesticide is intended to be applied directly to food or to material/article for the purpose of treating food
- Indirect food use: Application of antimicrobial in/on material/article that comes into contact with food but use is not intended for pesticidal treatment of food

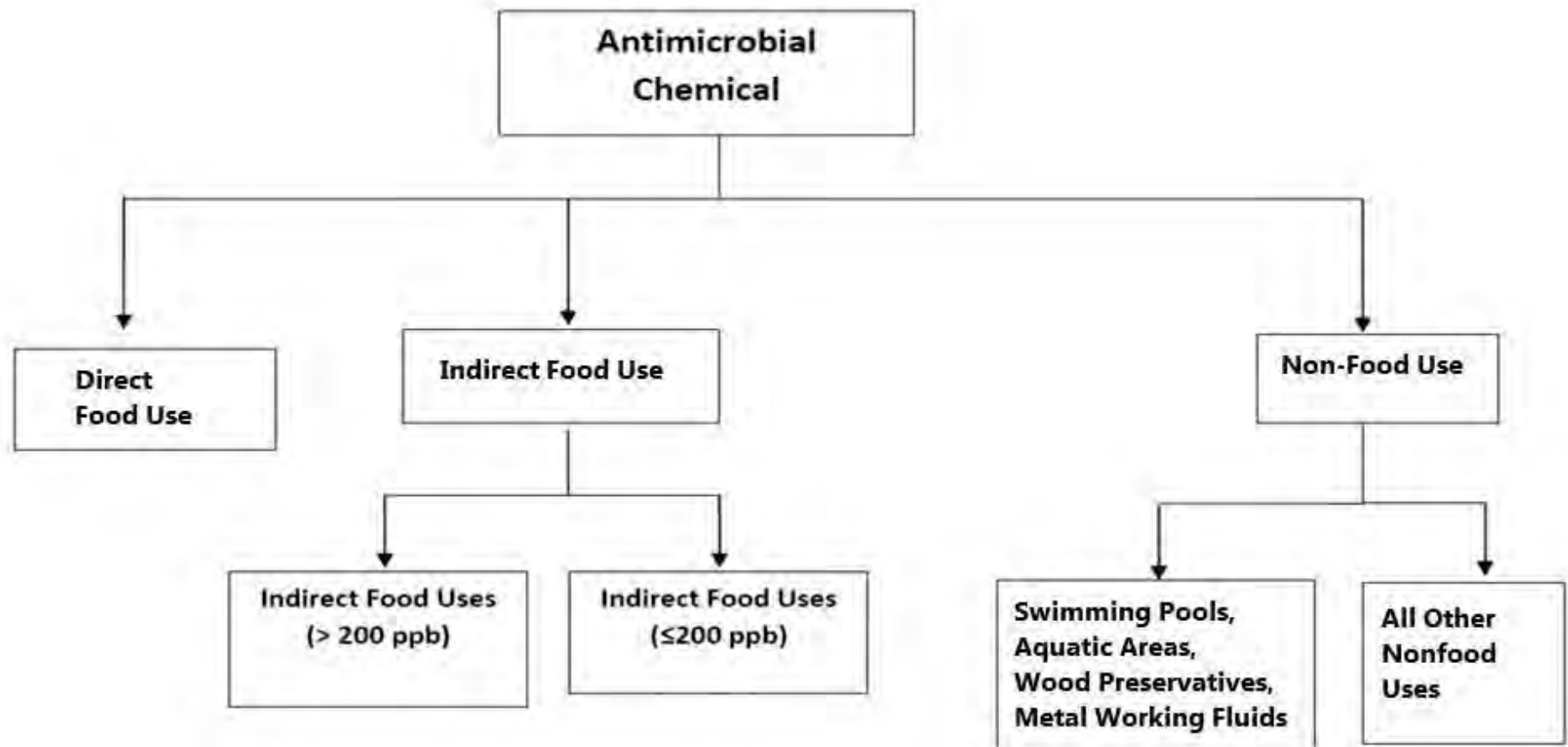


Dietary Assessment

- 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
- Drinking water exposure can occur from anything that may go down-the-drain, from drinking water treatment, or from industrial discharges
- Potential concerns for human exposure to antimicrobials from ingestion of drinking water could trigger toxicology data requirements



Toxicology Data Requirements Decision Tree





Determining Toxicology Data Requirements

- First determine the major use pattern from the USI.
- Second, determine the specific use site(s) for the antimicrobial pesticide.
- Third, determine whether there is potential for exposure to the antimicrobial from direct food use, indirect food use or non-food use.
- Next, consult the appropriate column of the toxicology data requirements table to applicable data requirements.
- Generally, direct food uses, indirect food uses where total dietary residue from the use is $> 200\text{ppb}$, and certain specific uses (swimming pools, wood preservatives, metalworking fluids, aquatic areas) require the most toxicology data than indirect food uses where total daily dietary residue is less than or equal to 200 ppb and “all other nonfood uses”.



Important Points on Toxicology Data Requirements

- Note that for any antimicrobial use pattern, there are core toxicology data that are always required:
 - Acute toxicity battery (6-pack)*
 - Mutagenicity testing battery
 - 90-Day toxicity - rodent
 - Developmental Toxicity – two species (rat and rabbit preferred)
 - Reproduction and fertility effects
 - Immunotoxicity

*The agency has published guidance for when these studies can be waived. This guidance is available at

<https://www.epa.gov/pesticide-registration/bridging-or-waiving-data-requirements>



Important Points on Toxicology Data Requirements

- Required studies are listed in the table as (R). Required studies will always include the core data and, depending on the use site(s), additional toxicology data would potentially be required. For example, as noted in the toxicology data requirements table, swimming pool, wood preservative, metalworking fluid, and aquatic areas uses require toxicology data in addition to the core toxicology data.
- Again, the use pattern and specific use site(s) should be examined to determine the data required.



Conditional Toxicology Data Requirements

- Toxicology studies in addition to the core studies and any other required studies may also be conditionally required, designated as CR in the data requirements table. The test notes in the toxicology data requirements table explain conditions under which these data are or are not required.
- For example, a study may be 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.
- A study may be designated as CR based on the potential to reduce 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).



Important Points on Toxicology Data Requirements

158W contains two new toxicology data requirements:

- Developmental neurotoxicity test (870.6300)- a conditionally required study
- Immunotoxicity test (870.7800) - a required study for all uses.



Toxicology Data Requirements- Examples





Example #1: Direct Food Use (fruit and vegetable wash)

- **Direct** food use: A use is considered to be a direct food use if an antimicrobial pesticide is used to **directly treat food and/or food sources and as a result, finite residues in or on food are expected or reasonably likely to result**. A fruit and vegetable wash will be expected to have finite residues of the pesticide.
- The data requirements for a direct food use are similar to those needed for agricultural pesticides. This is because a direct food use is interpreted the same, whether the pesticide is an agricultural or antimicrobial pesticide. In both cases, **finite residues in or on food are expected or reasonably likely to result**.
- The column header “Direct food uses” would be used in this example to determine the required and conditionally required data.



Toxicology Data Requirements: 158.2230

Guideline Number	Data Requirement	Food Uses			Nonfood Uses		Test Substance to Support		Test Note No.
		Direct Food Uses	Indirect Food Uses (> 200 ppb)	Indirect Food Uses (≤ 200 ppb)	Swimming Pools, Aquatic Areas, Wood Preservatives, Metal Working Fluids	All Other Nonfood Uses	MP	EP	
Acute Testing									
870.1100	Acute oral toxicity – rat	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2
870.1200	Acute dermal toxicity	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.1300	Acute inhalation toxicity - rat	R	R	R	R	R	MP and TGAI	EP and TGAI	2, 4
870.2400	Primary eye irritation - rabbit	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.2500	Primary dermal irritation	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.2600	Dermal sensitization	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3, 5
870.6200	Acute neurotoxicity - rat	R	R	CR	R	CR	TGAI	TGAI	6, 11
Subchronic Testing									
870.3100	90-Day oral toxicity - rodent	R	R	R	R	CR	TGAI	TGAI	8, 9, 15, 38
870.3150	90-Day oral toxicity - nonrodent	R	R	CR	R	CR	TGAI	TGAI	10, 15
870.3200	21/28-Day dermal toxicity	CR	CR	CR	CR	CR	TGAI	EP and TGAI	12, 13
870.3250	90-Day dermal toxicity	CR	CR	CR	CR	CR	TGAI	EP and TGAI	7, 13, 14, 15
870.3465	90-Day inhalation - toxicity - rat	CR	CR	CR	CR	CR	TGAI	TGAI	7, 15, 16, 17



Toxicology Data Requirements: 158.2230

Chronic Testing									
870.4100	Chronic oral toxicity - rodent	R	R	CR	R	CR	TGAI	TGAI	18, 19, 20
870.4200	Carcinogenicity – two rodent species – rat and mouse preferred	R	R	CR	R	CR	TGAI	TGAI	19, 21, 22
Developmental Toxicity and Reproduction									
870.3700	Prenatal developmental toxicity - rat and rabbit preferred	R	R	R	R	R	TGAI	TGAI	23, 24, 25, 26
870.3800	Reproduction and fertility effects	R	R	R	R	R	TGAI	TGAI	26, 27, 28, 29
870.6300	Developmental neurotoxicity	CR	CR	CR	CR	CR	TGAI	TGAI	28, 29, 30
Mutagenicity									
870.5100	Reverse mutation assay	R	R	R	R	R	TGAI	TGAI	31, 32
870.5300 870.5375	<i>In vitro</i> mammalian gene mutation	R	R	R	R	R	TGAI	TGAI	31, 33
870.5385 870.5395	<i>In vivo</i> cytogenetics	R	R	R	R	R	TGAI	TGAI	31, 34
Special Testing									
870.7485	Metabolism and pharmacokinetics	R	R	CR	R	CR	PAI or PAIRA	PAI or PAIRA	35, 39
870.7200	Companion animal safety	CR	CR	CR	CR	CR	NR	Choice	36
870.7600	Dermal penetration	CR	CR	CR	CR	CR	Choice	Choice	3, 37
870.7800	Immunotoxicity	R	R	R	R	R	TGAI	TGAI	8



Example #2: Indirect Food Use (kitchen countertop use)

- A use is considered to be an **indirect** food use if food may come into contact with an antimicrobial pesticide, **but the pesticide is not intended to be applied directly to food**. 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 in or on food.

In this example, a kitchen countertop may contain an antimicrobial pesticide that is incorporated into the countertop 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.

- 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 (i.e. is the total daily dietary residue $>$ or \leq 200ppb?).



Example #2: Indirect Food Use (kitchen countertop use)

- Similar to the example for direct food use, the toxicology data requirements table is consulted to determine the data requirements under the 'indirect food uses (>200ppb)' column or the 'indirect food uses (\leq 200ppb)' column, as appropriate.
- Toxicology data where dietary residue > 200ppb will be the same as required for a direct food use. In the majority of cases for an indirect food use, total daily dietary residue is \leq 200ppb and less data would be expected to be required.



Toxicology Data Requirements 158W

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Acute Testing									
870.1100	Acute oral toxicity – rat	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2
870.1200	Acute dermal toxicity	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.1300	Acute inhalation toxicity - rat	R	R	R	R	R	MP and TGAI	EP and TGAI	2, 4
870.2400	Primary eye irritation - rabbit	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.2500	Primary dermal irritation	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3
870.2600	Dermal sensitization	R	R	R	R	R	MP and TGAI	EP and TGAI	1, 2, 3, 5
870.6200	Acute neurotoxicity - rat	R	R	CR	R	CR	TGAI	TGAI	6, 11
Subchronic Testing									
870.3100	90-Day oral toxicity - rodent	R	R	R	R	CR	TGAI	TGAI	8, 9, 15, 38
870.3150	90-Day oral toxicity - nonrodent	R	R	CR	R	CR	TGAI	TGAI	10, 15
870.3200	21/28-Day dermal toxicity	CR	CR	CR	CR	CR	TGAI	EP and TGAI	12, 13
870.3250	90-Day dermal toxicity	CR	CR	CR	CR	CR	TGAI	EP and TGAI	7, 13, 14, 15
870.3465	90-Day inhalation - toxicity - rat	CR	CR	CR	CR	CR	TGAI	TGAI	7, 15, 16, 17



Toxicology Data Requirements, cont.

Chronic Testing									
870.4100	Chronic oral toxicity - rodent	R	R	CR	R	CR	TGAI	TGAI	18, 19, 20
870.4200	Carcinogenicity – two rodent species – rat and mouse preferred	R	R	CR	R	CR	TGAI	TGAI	19, 21, 22
Developmental Toxicity and Reproduction									
870.3700	Prenatal developmental toxicity - rat and rabbit preferred	R	R	R	R	R	TGAI	TGAI	23, 24, 25, 26
870.3800	Reproduction and fertility effects	R	R	R	R	R	TGAI	TGAI	26, 27, 28, 29
870.6300	Developmental neurotoxicity	CR	CR	CR	CR	CR	TGAI	TGAI	28, 29, 30
Mutagenicity									
870.5100	Reverse mutation assay	R	R	R	R	R	TGAI	TGAI	31, 32
870.5300 870.5375	<i>In vitro</i> mammalian gene mutation	R	R	R	R	R	TGAI	TGAI	31, 33
870.5385 870.5395	<i>In vivo</i> cytogenetics	R	R	R	R	R	TGAI	TGAI	31, 34
Special Testing									
870.7485	Metabolism and pharmacokinetics	R	R	CR	R	CR	PAI or PAIRA	PAI or PAIRA	35, 39
870.7200	Companion animal safety	CR	CR	CR	CR	CR	NR	Choice	36
870.7600	Dermal penetration	CR	CR	CR	CR	CR	Choice	Choice	3, 37
870.7800	Immunotoxicity	R	R	R	R	R	TGAI	TGAI	8



Example #3: Non Food Use

- A use is considered **nonfood** if there is **no reasonable expectation of finite residues in food based on the application of an antimicrobial pesticide**.
- This definition is based on the presumption that food and/or food sources will not come into contact with the pesticide chemical based on the use pattern.
- Use sites that fall into this category include, but are not limited to:
 - Fuel tanks, human footwear, or nonfood areas (e.g., under the sink) of eating establishments.
- Tolerances and/or exemptions are not required for these non-food uses.



Example #3: Non-Food Use

- The toxicology data requirements table can be examined for the requirements for specific non–food use patterns and use sites (swimming pools, aquatic areas, wood preservatives, metalworking fluids) , and the requirements for ‘All other non-food uses.’
- Based on the magnitude and duration of human exposure certain **specific** non-food use patterns and use sites (metalworking fluid use, swimming pool use, wood preservative use, aquatic areas) require the same toxicology data as a direct food use.



Toxicology Data Requirements 158W

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870.7600	Dermal penetration	CR	CR	CR	CR	CR	Choice	Choice	3, 37
870.7800	Immunotoxicity	R	R	R	R	R	TGAI	TGAI	8



Attributes of Test notes

- Test notes may describe studies that are required on the basis of findings from the “Core” toxicology data.
- Test notes may also describe specific requirements for specific uses.
- Test notes may describe approaches that can result in reduction in animal usage for a specific data requirement.



Attributes of Test Notes

- An example of a test note that may describe studies that are required on the basis of findings from the “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 required for non-food uses and for indirect food uses where total dietary residue is ≤ 200 ppb.
- An example of a test note that may describe specific requirements for a specific use is testnote 15. The 90-day oral toxicity study, 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 inhalation and one by dermal, are required. This is based on the exposure from the HVAC use being primarily by the dermal and inhalation routes.



Attributes of Test Notes

- An example of a test note that describes an approach that can result in reduction in animal usage for a data requirement is test note 8. Test note 8 states that:
“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.”
- Prior to initiating such combined studies, protocols should be submitted to the agency for review



Alternative Approaches to Fulfill Toxicology Data Requirements

The 158W Antimicrobial Pesticide data requirements rule allows for other approaches for addressing toxicology data requirements:

- Registrants can cite open scientific literature. OPP has developed guidance on the use and acceptability of open scientific literature for hazard characterization, available at: <http://www.epa.gov/pesticides/science/literature-studies.html>
- *In vitro* approaches can also be used to address acute toxicity data requirements (an alternative approach to assessment of eye irritation has been published by OPP at <http://www2.epa.gov/pesticide-registration/alternate-testing-framework-classification-eye-irritation-potential-epa>)
- Data on structurally related chemicals, including ((Quantitative) Structure-Activity Relationship ((Q)SAR) can also be cited.



Alternative Approaches to Fulfill Toxicology Data Requirements

In using alternative approaches, the registrant must submit all relevant information and/or data and state clearly why the approach is a valid alternative approach.

- The information must be relevant to evaluating the chemical's end-point of concern (physical chemical property, environmental fate, or biological).
- It must be credible and scientifically valid;
- The basis for the results must be transparent and reproducible.

Specific details concerning the information that EPA could find useful when evaluating an SAR or QSAR are in the "NAFTA TWG Quantitative Structure Activity Relationships [(Q)SAR] Guidance Document".

<http://www.epa.gov/oppfead1/international/naftatwg/guidance/qsar-guidance.pdf>



For Further Information:

For further information and questions on mammalian toxicology data requirements for antimicrobial pesticides, contact the Antimicrobials Division Ombudsman at:

OPP_AD_Ombudsman@epa.gov