EPA/OCSPP/OPP

Registration Division/Antimicrobials Division/Biopesticides and Pollution Prevention Division

STANDARD EVALUATION PROCEDURE (SEP) FOR CHEMISTRY AND ACUTE TOXICOLOGY SCIENCE ADVISORY COUNCIL (CATSAC)

Formerly known as Similarity Clinic

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Initiated By: _____ Date: 11/13/19

Print Name: Joseph Williams Jr.

Technical Review (CATSAC Co-Chairs)

_____ Date: 10/31/19

Print name: MARY Elissa Reaves

_____ Date: 10/31/2019

Print name: Tara Flint

_____ Date: 10/31/19

Print name: Lindsay ODell

Approved By:

_____ Date: _____

Print name: Anita Pease
Division Director, Antimicrobials Division

_____ Date: 10/31/2019

Print name: Michael Goodis
Division Director, Registration Division

_____ Date: 10/31/19

Print name: Anne Overstreet 11/7/19
Division Director, Biopesticides and Pollution Prevention Division

_____ Date: 10-31-19

Print name: Marcus Rindal
Quality Assurance Officer, Antimicrobials Division

_____ Date: 11/20/2019

Print name: D. Denise Rice
Director of Quality Assurance, Office of the Program Director

Effective Date: _____

Controlled Copy No: _____

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1.0 BACKGROUND

1.1 Overview

The Office of Pesticide Programs (OPP) within the U.S. EPA requires 6 different acute toxicity studies and product chemistry data as part of pesticide product registration requirements under 40 CFR 158.310[1] and 158.500.[2] However, 40 CFR 158.45 also provides the opportunity to grant waivers when the data are not informative for regulatory or public health protective decisions. OPP also relies on the 2012 OECD waiver guidance document and the 2016 acute dermal-oral bridging guidance. FIFRA provides definitions to identify products that are substantially similar, which may allow for citation or bridging of data requirements (details will be discussed further below and definitions are provided in Section 2 of this document).

The OPP began similarity determinations between products in 1991 and established the Similarity Clinic in 2012 (concurrently with PRIA 3) in response to the increasing number of similarity claims received. The Clinic's mission was to ensure consistency in the review of substantial similarity claims in regard to the citation of product chemistry and acute toxicity data as a basis for registration. In late 2016, the Similarity Clinic went through a reorganization and was re-named the Chemistry and Acute Toxicology Science Advisory Council (CATSAC), at which time the mission was also expanded to include efforts to reduce animal testing. The similarity determination process can reduce unnecessary study development and thereby reduce the number of animals required for testing. As described in the "OPP Director Jack Housenger letter to stakeholders," the Agency has committed itself to reducing animal testing and moving toward the replacement of traditional testing with alternative methods for the 6 pack studies. The CATSAC has become an integral component in achieving these goals.

The standard operating procedure (SOP) (ADM-03-01, dated 7/13/2017) for the CATSAC specifies that any scientific review rejecting the registrants' rationale for a similarity claim will be submitted to CATSAC for consideration. For products to qualify as identical/substantially similar "me-too" products, EPA applies the similarity criteria set forth in FIFRA Sections 3(c)(3)(B) and 3(c)(7)(A). Specifically, the pesticide product as proposed, must be identical or substantially similar in composition and labeling to a currently-registered pesticide, or differ in composition and labeling from such currently-registered pesticide only in ways that would not significantly increase the risk of unreasonable adverse effects on the environment.[1] (See also 40 CFR 152.113)[4] The OPP (and CATSAC) has the opportunity to expand beyond these identical and substantially similar evaluations to further reduce animal testing, and has begun to consider the bridging

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[1] Electronic Code of Federal Regulations. *Title 40: Protection of Environment* https://www.ecfr.gov/cgi-bin/text-idx?SID=f3a107ef5cf64d63b795b7e456c397de&mc=true&node=pt40.26.152&rgn=div5#se40.26.152_1113

[2] Environmental Protection Agency. *Pesticide Registration: Conditional Pesticide Registration* https://www.epa.gov/pesticide-registration/conditional-pesticide-registration

of acute toxicity data, which is expanded upon in this SEP document. For the remainder of this document, the term "identical or substantially similar" is used as shorthand for the full standard that includes "differ only in ways…".

1.2 Purpose & Scope

This Standard Evaluation Procedure (SEP) generally describes the evaluation process for the determination of products claiming to be identical or substantially similar for the purposes of relying upon previously submitted product chemistry and/or acute toxicology data, or for bridging acute toxicity data. This guidance is not a regulation and, therefore, does not add to, eliminate from, or change any existing regulatory requirements, nor can it be relied on to create any rights enforceable by any party in litigation with the United States Environmental Protection Agency. As such, it is not intended to be a checklist of factors or items that would always be required or not required. As described throughout the SEP, each similarity determination will be made on a case-by-case basis that reflects the active ingredients, solvents, inerts, and other constituents that are included in the product. This SEP is intended to be used by members of the CATSAC and staff from the Antimicrobials (AD), Biopesticides and Pollution Prevention (BPPD) and Registration Divisions (RD) for making similarity determinations for proposed pesticide registrations. This SEP provides guidance to the registrant community so that bridging rationale and/or identical and substantially similar packages submitted to the Agency include the pertinent and necessary information needed by submission reviewers and CATSAC members for their evaluation.

As outlined in the CATSAC Standard Operating Procedure (SOP) (ADM-03-01, dated 7/13/2017), any product chemistry or acute toxicity review from participating Divisions that questions or rejects the registrants' rationale for a similarity or data bridging claim should be submitted to CATSAC for review. Additionally, CATSAC may evaluate waiver requests on a case-by-case basis. The following Agency guidance documents may be referred to when discussing waivers: Guidance for Waiving or Bridging Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products, Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis.

The proceeding sections describe information and criterion CATSAC will consider when providing product chemistry and acute toxicology evaluations for any type of substantial similarity or data bridging determination.

2.0 DEFINITIONS

SEP- Standard evaluation procedure

OPP- Office of Pesticide Programs

AD- Antimicrobials Division

BPPD- Biopesticides and Pollution Prevention Division

RD- Registration Division

PRIA- Pesticide Registration Improvement Act

PM- Product Manager

CBI- Confidential Business Information

EP End-use product: A pesticide product whose labeling: (1) Includes directions for use of the product (as distributed or sold, or after combination by the user with other substances) for controlling pests or defoliating, desiccating or regulating growth of plants, or as a nitrogen stabilizer, and (2) does not state that the product may be used to manufacture or formulate other pesticide products.

MUP – Manufacturing use product: Any pesticide product other than an end-use product. A product may consist of the technical grade of active ingredient only, or may contain inert ingredients, such as stabilizers or solvents.

TGAI – Technical grade active ingredient: A material containing an active ingredient: (1) Which contains no inert ingredient, other than one used for purification of the active ingredient; and (2) Which is produced on a commercial or pilot plant production scale (if it is ever held for sale).

"Me-Too"- A "Me-Too" pesticide registration application refers to a request to register a new pesticide product that is identical in its uses and formulation or substantially similar in its uses and formulation to one or more products currently registered and marketed in the United States, or differing only in ways that would not significantly increase the risk of unreasonable adverse effects on the environment. These applications are also called "Fast Track New Products," though the preferred term consistent with FIFRA is "identical or substantially similar product."

100% Repack - A 100% identical re-packed product is one that is manufactured by repackaging another EPA registered product, with no changes to its composition. The labeling of the proposed product is the same in all relevant respects except for another registrant name, address, name of product and registration number. The proposed product may also choose to include a subset of the approved uses of the registered product.

3.0 PRODUCT CHEMISTRY EVALUATION PROCESS

3.1 Identical Products

A proposed pesticide Manufacturing Use Product (MUP) or End Use Product (EP) is generally considered "identical" to a registered pesticide product when all the following

conditions are met:

- Same active ingredient(s), with the same purity
- Same nominal concentration of active ingredient(s)
- Same nominal concentration of all inert ingredients
- Same certified limits for all active and inert ingredients
- Same single component inert ingredients
- Same inert[3] mixtures (mixtures have the same chemical composition)
- No added or deleted inert ingredients
- Same impurities with the same concentration
- The use patterns for the proposed product are the same as the registered product. The proposed product cannot have use patterns not claimed in the registered product.

3.2 Substantially Similar Manufacturing and End Use Products

A scientific judgment will be made via a qualitative assessment, primarily by comparing the physical-chemical properties and chemical composition of the proposed and cited products on a case-by-case basis. A proposed pesticide Manufacturing Use Product (MUP) or End Use Product (EP) will generally be considered "substantially similar" to a registered product when all of the following conditions are met:

- Same active ingredient(s)
- The nominal concentration of the active ingredient(s) is the same or within the certified limits of the cited product. A request for wider certified limits for the proposed product is permissible, however, a justification must be supplied by the registrant.
- Inert ingredients need not be identical; however, the inert ingredients should not differ such that the physical and chemical properties would change when compared to the cited product. Inert ingredients, including all components and safeners of a mixture and/or the trade name must be cleared/evaluated by the Inert Ingredient Assessment Branch (IIAB) of the Registration Division and have the same cleared/evaluated uses as the cited product.
- There should be NO changes to the Label warning under the Physical or Chemical Hazards [See 40 CFR 156.78 for the various Label warnings required.].
- The proposed product bears the same use patterns (or subset of) as the cited, registered product. Please note that if use patterns are added or substituted on the proposed product label, then it is no longer considered substantially similar to the cited product.

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[3] Environmental Protection Agency. *Pesticide Registration: Inert Ingredients Overview and Guidance* https://www.epa.gov/pesticide-registration/inert-ingredients-overview-and-guidance#inertfinder

Examples of product formulations considered to be substantially similar and non-substantially similar are found in Appendix 5.1.

3.3 Substantially Similar Technical Grade Active Ingredient (TGAI)

A proposed TGAI will generally be considered substantially similar to a registered TGAI when all of the following conditions are met:

- Same active ingredient
- The proposed TGAI must not contain impurities of toxicological significance (e.g., nitrosamines, dioxins, etc.), which are not present in the registered chemical. If the proposed TGAI has any impurity of toxicological significance which is not present in the cited product, then the proposed TGAI is deemed "not substantially similar" from a compositional point of view.
- If the same impurities of toxicological significance are present in the proposed TGAI, the impurity's upper certified limit must be equal or less than the registered chemical.
- When there are additional or different impurities of unknown toxicity present in the proposed TGAI when compared to the cited TGAI, the proposed product will be subjected to risk assessment. After the risk assessment of impurities is complete, a determination of substantial similarity will be made. Impurities of known toxicological significance should be identified [See 40 CFR 158.320c].

3.4 Product Chemistry Data Requirements

Unless identical in composition every proposed EP application must provide product specific data addressing the product chemistry 830 guidelines listed in Product Chemistry Data Requirements of the 40 CFR 158.310. The analytical method may be cited. However, the Physical and Chemical Properties data can be submitted in the application according to PR Notice 98-1 (self- certification).

- If the source of the TGAI in the proposed MUP or EP is not a registered source of the active ingredient; then product chemistry 830 series guideline's[4] Product Chemistry Data Requirements must be provided on that specific source of the active ingredient (no cited data) as well as the proposed end use product. The analytical method for the active ingredient may be cited.

[4] Environmental Protection Agency. *Test Guidelines Pesticides and Toxic Substances Series 830 Product Properties Test Guidelines*
https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-830-product-properties-test-guidelines

4.0 ACUTE TOXICOLOGY EVALUATION PROCESS

If the proposed and cited products are **identical** (100 % in AI and inert or repack) in composition (as laid out in previous section), then it is not necessary to send the PRIA action to the CATSAC, and the review can be handled by the product manager (PM) team. If the proposed and cited products are not identical, any questions or rejections by the reviewer within a Division regarding substantial similarity or the registrant's data bridging rationale, then the case should be sent to CATSAC for review, as consistent with the CATSAC SOP.

4.1 Toxicologically Substantially Similar Products

Specific quantitative parameters cannot be established to classify those products distinguished as substantially similar, given the unique formulations and toxicological profiles for each case reviewed. CATSAC was established to provide a framework for discussion and consideration of the scientific weight of evidence for each individual submission including questions regarding substantial similarity or data bridging. While specific brackets or cut-off levels cannot be established, there are product characteristics that are generally examined by the Division reviewers, and CATSAC if necessary, to deem whether a proposed MUP or EP is toxicologically substantially similar for purposes of citing previously submitted data. These characteristics may include, but, are not limited to the following conditions:

- The same active ingredient(s).
- The nominal concentration(s) of the active ingredient(s) in the proposed product should not exceed the upper certified limit(s) of the cited product(s). The cited product generally should not have a lower concentration than the proposed product. However, if the concentration of the cited product is lower than the proposed product, the potency of the active ingredient and the difference in concentration may be considered in the determination of the overall safety finding.
- The proposed product should not contain any additional active ingredients not found in the cited product(s). However, active ingredients that may be in the same chemical class should be considered in the context of the total amount of active ingredient in either the proposed or cited product.
- Uses of the proposed product and use classification should be the same as uses or a subset of the cited products use patterns and use classification.
- The proposed product should not contain additional inerts that are of toxicological significance and would contribute to acute toxicity profiling (example: methanol, preservatives, etc.).

  The proposed products label should be the same as the cited product(s) labeling, unless the cited products label has discrepancies that need to be addressed. Similar label language will be used for the proposed product, without the discrepancies.

4.2 Bridging Determinations for Toxicology

Bridging refers to the use of existing acute toxicity data of a registered product that will provide health protective labeling for the proposed product. Bridging of data may be considered by CATSAC when a substantial similarity claim was not supported or approved. The Agency may determine that the acute toxicity data of the cited product is sufficient to support registration of the proposed product, even if the two products were not deemed substantially similar. In some cases, submissions from the registrants may directly indicate that cited labels and acute toxicity data can be bridged to the proposed product label rather than making a substantially similar claim. In this type of submission, a justification for the acute toxicity bridging must be included in the submission. The cited product(s) must be currently or formerly registered products(s) with valid data.

These justifications may include but are not limited to the following conditions:

- If more than one registered product is being cited, and the acute toxicity profiles differ between the cited products, CATSAC will generally rely upon the study that has the most protective toxicity category and/or profile in determining appropriate label statements for the proposed product. See Appendix 5.3.
- If the signal word and/or precautionary statements for the cited product are incorrect, CATSAC will ensure the proposed product has the correct labeling that are in line with current Agency standards. Corrective actions for the cited product(s) labeling will also be taken at the appropriate time.

4.2.1 Inert Ingredients

Inert ingredients need not be identical between the proposed and cited product, however, a change in the inert(s) should not change the toxicity, or physical/chemical properties of the proposed product relative to the cited product(s).[1]

Cases in which the differences in concentration and identity of inert ingredients may change the toxicity profile will be evaluated on a case-by-case basis using weight of scientific evidence. The following factors may be considered (but not limited to):

- Unique inert ingredients which are present in the proposed product but absent in the cited product.
- Inert ingredients of toxicological concern
- Change in pH (corrosive vs. non-corrosive, alkaline vs. acidic)
- Aqueous solvents vs. organic solvents

4.2.2 Product Citations

If a proposed product cites two different registered products with their own sets of acute toxicity data; the same active ingredients and inerts, but with different concentrations (one higher and one lower than the proposed product; i.e. the data bookends the proposed product); and the same toxicity categories by an exposure route; then the proposed product will be assigned the same toxicity categories as the cited products.

4.2.3 Diluted Products

If a proposed product is a dilution with water of the cited product with the same inert ingredients, the proposed diluted product will have the same precautionary labeling as the cited product, if no data have been presented to suggest otherwise. It may not be possible to estimate or quantify the reduction in toxicity profile and therefore determine appropriate label statements different than the cited product. If reduced labeling statements are requested by the registrant, then an appropriate substantially similar diluted product label or specific data similar to the diluted product should be cited.

4.2.4 Bridging Considerations

The process of bridging data will be determined on a case-by-case basis. The following are some of the considerations when *denying* a bridging request:

- If the registrant fails to provide a rationale for why the bridging request is applicable to the proposed product.
- If the proposed product contains additional active ingredients with toxicity profiles that are significantly different relative to the cited product(s).
- If the proposed product contains an inert ingredient of toxicological concern not present in the cited product(s).
- If the inert profile of the proposed product (based on the weight of scientific evidence) is deemed more potent or hazardous than that of the cited product(s).[1]

Note: A complete set of six acute toxicity studies is not required to make a bridging claim. A registrant may submit the appropriate study (or studies) in support of a claim that the proposed product has a reduced hazard potential by one or more exposure routes relative to the cited product(s).

5.0 APPENDICES

Note: The content below is provided for example purposes only and does not reflect the determination of an actual case. Each submission will be assessed on a case-by-case basis. The variations and ranges of concentrations of active and inert ingredients used in these examples are not intended to be prescriptive for all determinations. The differences in concentrations and potency of each ingredient is considered individually; specific ranges of (+/- 5% for instance) are not applied as a broad rule. A weight of evidence is used for each determination and the relevant factors contributing to the determination are mentioned in the comment section of the table for clarity.

5.1 Product Chemistry Similarity Examples

Table A: Substantially similar products for product chemistry

Criteria		Product A (Cited)	Product B (Proposed)	Comment
Physical/Chemical Property	**pH**	5	6	Both pHs are acidic
	Flammability	>100°C	125°C	Both are non-combustible
	Formulation	Liquid	Liquid	
	Solubility	Miscible in water	Miscible in water	
Ingredients	**Active Ingredient**	XY123	XY123	
	Conc. of AI	8%	7.5%	Nominal concentration of Product B is within the certified limits of the cited product
	Solvent	75% Water	80.5% Water	Differences of inert ingredients in Product B do not change the physical/chemical properties in comparison to cited
	Solvent	10% Organic	none	
	Surfactant	4%	5%	
	Chelating agents	2%	4%	
	Stabilizer	1%	2%	
	pH adjuster	None	1%	

Rationale:

The example presented in Table A demonstrates a substantially similar determination from a product chemistry point of view. In the case of having differences between the cited and proposed products, a weight of scientific evidence is used to determine if the physical and chemical properties differ significantly. In this example, CATSAC determined that Product A is substantially similar to Product C.

Table B: Non-Substantially similar products for product chemistry				
Criteria		**Product A (Cited)**	**Product C (proposed)**	**Comment**
Physical/Chemical Property	**pH**	5	8	Acidic to basic
	Flammability	>100°C	90°C	Hazard statements change on label
	Formulation	Liquid	Liquid	
	Solubility	Miscible in water	Miscible in water	
Ingredients	**Active Ingredient**	XY123	XY123	
	Conc. of AI	8%	4.5%	Nominal concentration not within certified limits of cited product
	Solvent	75% Water	65% Water	Differences in the concentration of inert ingredients may change the physical and chemical properties of the proposed product.
	Solvent	10% Organic	18.5% Organic	
	Surfactant	4%	5%	
	Chelating agents	2%	none	
	Stabilizer	1%	5%	
	pH adjuster	none	7%	

Rationale:

The example presented in Table B demonstrates a non-substantially similar determination from a product chemistry point of view. In the case of having differences between the cited and proposed products, a weight of scientific evidence is used to determine if the physical and chemical properties differ significantly such that the two are not similar. In this example, CATSAC determined that Product A is not substantially similar to Product C.

5.2 Acute Toxicology Similarity Examples

Table C: Toxicological substantially similar products				
Criteria		**Product A (Cited)**	**Product B (Proposed)**	**Comment**
Physical/Chemical Property	**pH**	5	3	Lower pH of Product B remains acidic, not corrosive
	Flammability	>100°C	>100°C	
	Formulation	Liquid	Liquid	
	Solubility	Miscible in water	Miscible in water	
Ingredients	**Active Ingredient**	XYZ 321	XYZ 321	Product B does not contain additional active ingredients
		ZYX 123		
	Conc. of AI	Total 15%	11%	Nominal concentration does not exceed upper certified limit of Product A
	Solvent	75% Water	80% Water	No additional inerts of toxicological significance are added to Product B
	Solvent	10% Organic	-	
	Surfactant	4%	2%	
	Surfactant		2%	
	Chelating agents	2%	-	
	Stabilizer	1%	-	
	pH adjuster	None	5%	

Rationale:

The example as presented in Table C demonstrates products that are substantially similar from a toxicological point of view. Although these products are not similar from a chemistry point of view (i.e., the amount and concentration of active ingredients), weight of scientific evidence is used to determine that cited products data would be health protective for the proposed product. In this example, CATSAC determined that the acute toxicity profile for Product A may be health protective of Product B.

Table D: Toxicological Non-Substantially similar products				
Criteria		**Product A (Cited)**	**Product C (Proposed)**	**Comment**
Physical/Chemical Property	**pH**	6	N/A	Physical property not comparable
	Flammability	>100°C	>100°C	
	Formulation	Liquid	Liquid	
	Solubility	Miscible in water	Immiscible in water	Significant change to physical property
Ingredients	**Active Ingredient**	JLO 800	JLO 800	
	Conc. of AI	10%	12%	Product C exceeds the upper certified limit of Product A
	Solvent	30% Water	10% Organic	Differences in concentration and identity of inert ingredients present in Product C may change the toxicity profile.
	Pigment	9.5%	35%	
	Resin	4%	32%	
	Surfactant	0.50%	-	
	Plasticizer	-	2%	
	Stabilizer	1%	-	
	Inert filler	45%	10%	

Rationale:

The example as presented in Table D demonstrates a non-substantially similar determination. Although these products are not similar from a toxicological point of view, a weight of scientific evidence is used to determine whether the cited products labeling would be health protective for the proposed product. In this example, CATSAC determined that the acute toxicity profile for Product A may not be health protective of Product C, mainly due to the differences in inert ingredients, thus, bridging is not accepted.

Table E: Toxicological Bridging determination				
Criteria		**Product A (Cited)**	**Product C (Proposed)**	**Comment**
Physical/Chemical Property	**pH**	6.5	3-4	
	Flammability	>80°C	>170°C	
	Formulation	Liquid	Liquid	
	Solubility	Miscible in water	Miscible in water	
Ingredients	**Active Ingredient**	CATZ 2000	CATZ 2000	
	Conc. of AI	60%	25%	Proposed is significantly less than cited.
	Solvent(s)	15% Water 15% Organic	50% Water 10% Organic	Proposed product is more diluted in water.
	Pigment	-	5%	
	Surfactant	2%	-	
	Plasticizer	5.5%	-	
	Stabilizer	1%	-	
	pH Adjuster	1.5%	10%	

Rationale:

The example as presented in Table E demonstrates a non-substantially similar determination. Although these products are not similar from a toxicological point of view, a weight of scientific evidence is used to determine whether the cited products labeling would be health protective for the proposed product. In this example, CATSAC determined that the acute toxicity profile for Product A is health protective of Product C, mainly due to the differences in active ingredient concentration and water, thus, bridging is accepted.

5.3 Protective Labeling

Table F: A comparison of acute toxicity categories for the acute toxicity studies for the various cited products compared to the proposed product.

	PRODUCT A	PRODUCT B	PRODUCT C	**PROPOSED PRODUCT LABELING**
ACUTE ORAL	II	I	II	**I**
ACUTE DERMAL	II	II	II	**II**
ACUTE INHALATION	I	I	III	**I**
EYE IRRITATION	I	I	I	**I**
SKIN IRRITATION	II	III	II	**II**
SKIN SENSITIZATION	SENSITIZER	SENSITIZER	NON-SENSITIZER	**SENSITIZER**

Rationale:

The example presented in Table F demonstrates how the acute toxicity categories for substantially similar cited products compare across the group. In cases where multiple products are cited, and all are deemed substantially similar, the most health protective toxicity category should be assigned for the proposed label. Therefore, in this example the proposed products labeling for acute oral toxicity would receive a category I based on Product B.