UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION#

MEMORANDUM

Date: **04/11/2019**

Subject: **Pyrethroids.** Documentation of the Systematic Literature Review Conducted in Support of Registration Review.

PC Code: See Table
Decision Nos.: 543196
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: NA

DP Barcode: D448870
Registration No.: Numerous
Regulatory Action: Registration Review
Case No.: NA
CAS No.: See Table
40 CFR: See Table

From: Robert McGovern, Chemist
Krystle Yozzo, Ph.D., Biologist
William Donovan, Ph.D., Chemist
Connor Williams, MHS, Toxicologist
Anwar Dunbar, Toxicologist
Austin Wray, Toxicologist
Kristin Rickard, Biologist
Health Effects Division (HED; 7509P)

Through: Christina Swartz, Branch Chief
Risk Assessment Branch 2; HED (7509P)

To: HED Management Team
and
Evisabel Craig, Ph.D., Toxicologist
Risk Assessment Branch 6; HED (7509P)

Chemical	PC Code	CAS No.	40 CFR Reference
Bifenthrin	128825	82657-04-3	§180.442
Cyfluthrin	128831	68359-37-5	§180.436
Cypermethrin	109702	52315-07-8	§180.418
Cyphenothrin	129013	39515-40-7	NA
Deltamethrin	097805	52918-63-5	§180.435
Esfenvalerate	109303	66230-04-4	§180.533
Fenpropathrin	127901	39515-41-8	§180.466
Imiprothrin	004006	72963-72-5	NA
d-Phenothrin	069005	26002-80-2	§180.647
Prallethrin	128722	23031-36-9	§180.545
Pyrethrin	069001	8003-34-7	§180.128
Tau-Fluvalinate	109302	102851-06-9	§180.427
Tetramethrin	069003	7696-12-0	NA

1.0 Executive Summary

The Health Effects Division's (HED)'s Management Team assigned a workgroup to conduct a systematic review of publicly available literature on pyrethroids. The objective was to identify studies which would potentially have an impact upon the route-specific endpoints used in pyrethroid human health risk assessments. Identification of these studies involved a tiered review approach to eliminate studies which did not meet specific requirements for methodology, test subjects, test substances, relevance to human exposures, and dose levels sufficiently low to potentially result in the selection of lower points of departure (PODs) used for individual pyrethroid risk assessments. Studies found to pass the screening criteria were forwarded to the appropriate pyrethroid risk assessment teams for consideration.

2.0 Systematic Review and Data Collection Background

In recent years, the National Academy of Sciences (NAS) National Research Council (NRC) has encouraged the Agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making (NRC, 2011). The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies" (NRC, 2014). Consistent with NRC's recommendations, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) is currently developing systematic review policies and procedures. In short, OCSPP employs "fit for purpose" systematic reviews that rely on standard methods for ***collecting, evaluating, and integrating*** scientific data to support the Agency's decisions. The concept of "fit for purpose" implies that a particular activity or method is suitable for its intended use. Inherent in this definition is the concept that one size does not fit all situations and thus flexibility is allowed. However, it is notable that with flexibility comes the importance of transparency of documented processes; including the importance of transparency and clarity in approaches to data collection, evaluation, and integration.

A systematic review for considering open literature studies into human health risk assessment begins with a problem formulation to determine the scope and purpose of the search. Studies are

considered based on their relevance to answer specific questions and those studies deemed relevant are then further considered for their usefulness in risk assessment.

The Agency strives to use high-quality studies when evaluating the hazard potential of pesticidal chemicals and considers a broad set of data during this process. This includes registrant generated studies required under FIFRA, as well as peer-reviewed scientific journals and other sources, such as other governments and academia. A wide range of potential adverse effects are assessed using acute, subchronic, chronic, and route-specific studies (predominately from studies with laboratory animals); in addition to epidemiologic and human incident data. All studies are thoroughly reviewed to ensure appropriate conduct and methodologies were utilized, and that sufficient data and details are provided. In this way, hazards are identified and potential risks characterized to ensure that Agency decisions are informed by the best science available. This document details the methods and criteria by which studies were reviewed.

2.1 Workgroup Task

This systematic review is inclusive of naturally occurring pyrethrins and synthetic pyrethroids, are a broad class of synthetic insecticides, closely related to naturally occurring compounds produced by chrysanthemums. As part of the pyrethroid registration review process, HED conducted a review of the open literature to confirm that the pyrethroid human health risk assessments accounted for mammalian toxicity reported for this chemical class. Specifically, HED was interested in any animal laboratory studies in which a toxic response to pyrethroids was observed at doses lower than the currently selected points of departure for human health risk assessment purposes. The review was conducted using a systematic approach to parse the large body of pyrethroid literature for studies that were most likely to impact risk assessment (see section 3.0 for a graphical depiction). Epidemiology studies identified during this review were provided to epidemiologists for review. In general, this approach follows the "Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment" (8/28/2012, Office of Pesticide Programs, U.S. Environmental Protection Agency). The search strategy and tagging process (Section 2.2), study prioritization and abstract/full text screen including exclusion/inclusion criteria (Section 2.3), and the results of the review (Section 2.4) are detailed below.

2.2 Search Strategy and Tagging

HED employed a generalized, inclusive search strategy to generate a comprehensive list of pyrethroid citations. The search was conducted in PubMed on 05/16/2017 using the following search terms without restriction on publication date or language:

> (Pyrethroid OR Deltamethrin OR Bifenthrin OR Cyfluthrin OR Cypermethrin OR Cyphenothrin OR "d-Phenothrin" OR Esfenvalerate OR Fenpropathrin OR Imiprothrin OR Prallethrin OR Pyrethrin OR Tau-Fluvalinate OR Tetramethrin)

This search strategy returned 10332 citations. Due to the size of the citation list, HED elected to categorize the citations based on model organism prior to screening for relevance. Study categorization was performed using the tagging and search functions in the SWIFT-Review

software (Sciome Workbench for Interactive computer-Facilitated Text-mining v. 9.18.2017; https://www.sciome.com/swift-review/). Studies imported into the software were automatically categorized based on model organism using a software-driven tagging process that searches for pre-defined keywords in the title, abstract, and Medical Subject Headings (MeSH terms). HED then applied unique tags to each study using the search function and a combination of the model organism tags, and keywords and MeSH terms for mammalian models, human models, and alternative mammalian models. The studies were grouped into the following subsets: common non-human mammalian models (1990 citations; including, but not limited to, rats, mice, dogs, and rabbits), other non-human mammalian models (1818 citations), human models (950 citations), alternative mammalian models (191 citations; include nematodes, fruit fly, and zebrafish studies), or animal models not tagged in the other categories (3891 citations). Studies not included in one of these five categories lacked information identifying them as an animal or human toxicity study; therefore, they were not anticipated to contain relevant information and were excluded from the review (1532 citations).

2.3 Prioritization and Title/Abstract Screen

HED prioritized screening of the "common mammalian model" and "other mammalian model" studies for review because it was determined during the tagging process that these subsets were the most likely to contain relevant animal laboratory data that could inform risk assessment. The "alternative mammalian model" and "human model" subsets were not screened because they were less likely to contain information relevant to the review question. The "animal models not tagged in the other categories" subset was less defined than the other four subsets and there was uncertainty as to the nature and types of citations included in the subset. A separate preliminary screen of this subset was conducted to determine if it should be subject to the rigorous screening process employed for the two prioritized subsets.

In order to best inform the human health risks posed by pyrethroids, the literature review team utilized a set of core inclusion/exclusion criteria to ensure that a study was relevant for human exposure to pyrethroids and useful for risk assessment. Each study's methodology, test subjects (mice, rats, cell line, etc.), test substances (i.e., individual pyrethroid active ingredients), relevant exposure pathways, and appropriate dose levels were compared to the current pyrethroid active ingredient's database. The general inclusion and exclusion criteria are provided in Table 1.

Table 1. General Inclusion/ Exclusion Criteria

Evidence Stream	Inclusion Criteria	Exclusion Criteria (or blank if none)
Participants/Population (Human Studies or Experimental Model Systems)		
Human	– No restrictions on sex, age, life stage (including *in utero* exposure) at time of exposure or outcome assessment – No restrictions on country of residence/origin, lifestyle, race/ethnicity, or occupation	– Epidemiology studies[1]

Table 1. General Inclusion/ Exclusion Criteria		
Evidence Stream	**Inclusion Criteria**	**Exclusion Criteria (or blank if none)**
Animal	– No restrictions on sex, age, mammalian species, or life stage at exposure or outcome assessment	– Mechanistic *in vitro* studies[2] – *In vivo* studies conducted with alternative mammalian models (*D. rerio*, *C. elegans*, *Drosophilla* spp., etc.)[3] – *In vivo* studies conducted with non-mammalian models (e.g., plants, fungi, protists, algae, birds, fish, etc.)
Exposure		
Human or Animal	– Exposure to the a.i. is defined based on administered dose or concentration, bio-monitoring data (e.g., urine, blood, or other specimens), environmental measures, or indirect measures – Information on exposure duration is provided – Route of administration is relevant to human health risk assessment (e.g. oral, dermal, or inhalation)	– Studies that failed to quantify exposure levels or lack exposure information – Mixture studies that do not report on toxicity from exposure to the a.i. only – Studies which were conducted using doses which were not anticipated to impact current risk assessments – Studies which used dosing methods not relevant to human exposure, such as intraperitoneal injection
Comparators		
Human	– Humans exposed to lower levels (or no exposure/exposure below detection levels) of the a.i.	
Animal	– Study must include concurrent vehicle or untreated control group(s)	
Outcomes		
Human and Animal	– No restrictions on toxicological outcomes	– Studies that do not discuss toxicological outcomes related to exposure including those that only report data on

Table 1. General Inclusion/ Exclusion Criteria		
Evidence Stream	**Inclusion Criteria**	**Exclusion Criteria (or blank if none)**
		absorption, distribution, metabolism, and excretion (ADME)[4]
Publications (e.g., language restrictions, use of conference abstracts, etc.)		
Human and Animal	− Studies reporting original data	− Articles with no original data (e.g., editorial or review)[5] − Studies published in abstract form only (grant awards, conference abstracts) − Retracted articles − Non-English language articles that cannot be categorized based on English abstract[6]

[1]Epidemiology studies were flagged during screening for consideration in HED's epidemiology review.
[2]*In vitro* studies were excluded from the general toxicology literature review; however, during the screen, these studies were flagged in the event further review is warranted.
[3]*In vivo* studies conducted with alternative mammalian models were excluded from the general toxicology literature review; however, during the screen, these studies were flagged in the event further review is warranted.
[4]ADME/pharmacokinetics studies were excluded from the general toxicology literature review; however, during the screen, these studies were flagged in the event further review is warranted.
[5]Relevant reviews were used as background and for reference scanning.
[6]Studies published in a language other than English were screened to the extent they could be without full translation. A full translation was pursued only if it was determined that the study contains information that impacts risk assessment.

2.4 Iterative Review

The screened studies were compared against the inclusion and exclusion criteria by a team of scientists in a tiered review approach, with iterative increases to the level of the review starting at title/abstract and proceeding to full text. A flowchart has been generated to summarize the process (Section 3.0).

The preliminary screen of the "animal models not tagged in the other categories" was conducted by a single reviewer and examined 1200 of the 3891 citations from this subset (targeted review of the newest studies, from 2012-2017). The preliminary screen identified 6 studies which potentially had relevance to the pyrethroids risk assessments; however, a more detailed investigation of the full text found that all 6 of these studies should be excluded. The team extrapolated that the remaining studies from this subset were anticipated to provide negligible value. The remaining 2691 studies from this subset were determined to most likely be uninformative to the risk assessments, and therefore were excluded from further screening.

The title and abstract of the citations in the prioritized subsets were fully screened by two reviewers, separately and independently. The results of each reviewers' independent analyses of the title and abstracts for each study were compared. Discrepancies were investigated in further detail, and resolved. At the end of this review, 197 total studies were identified for full text (second level) review. In total, 5008 of the 10352 citations were screened.

The second level of review separated the 197 studies by the pyrethroid compounds they investigated (for example, all deltamethrin studies were grouped together). Studies containing multiple compounds were assigned to a separate group, and human exposure monitoring studies (such as on farm workers and others exposed to pesticides in home or workplace) were assigned to another unique group. Each group was then assigned to a primary and a secondary reviewer, who each did an independent full text review. As before, any discrepancies were reconciled. At the end of this review, 48 studies were identified forwarded as candidates for the next (third) level of review. However, it was discovered that 1 study (Wolansky et al., 2006) has been previously reviewed by HED and the results of the study used to establish points of departure (PODs) for numerous compounds, and as such, would not be re-reviewed during this process.

The third level of review used the Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (8/28/2012). The 47 remaining studies from the full-text review were subjected separately to these criteria by SIMB (Science Information Management Branch). Of these 47, the following 2 were forwarded to the respective chemical teams for consideration in risk assessment:

- Pine et. al. The pyrethroid pesticide esfenvalerate suppresses the afternoon rise of luteinizing hormone and delays puberty in female rats. Environ Health Perspect. 2008 Sep;116(9):1243-7.
- Farag et. al. Effects of permethrin given before mating on the behavior of F1-generation in mice. Neurotoxicology. 2006 27;3:421-428.

Additionally, two articles was identified which HED has already reviewed and incorporated into human health risk assessments.

- Wolansky et al. Relative potencies for acute effects of pyrethroids on motor function in rats. Toxicol Sci. 2006 Jan;89(1):271-7.
- Moser et. al. Locomotor activity and tissue levels following acute administration of lambda- and gamma-cyhalothrin in rats. Toxicol Appl Pharmacol. 2016 Dec 15;313:97-103.

3.0 Visual Flowchart