OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

DATE: 18-APR-2024

SUBJECT: **Cyflumetofen. Updated Scoping Document:** Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review.

PC Code: 138831
CAS No.: 400882-07-7
Petition No.: NA
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

Task Group No.: 00606731
Parent Case No.: 00485319
Registration No.: NA
Regulatory Action: Registration Review Scoping Document
Reg. Review Case No.: NA
40 CFR: §180.677

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The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: https://www.epa.gov/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions.

INTRODUCTION

Consistent with the Food Quality Protection Act of 1996, under FIFRA, the Health Effects Division (HED) is providing a scoping document for cyflumetofen in support of registration review. This updated scoping document provides a summary of the current risks associated with cyflumetofen and identifies data needs as well as anticipated risk assessments needed to support the registration review. Since the initial scoping document was completed in 2023, the final data needs for satisfying the Endocrine Disruptor Screening Program (EDSP) were determined and incorporated into this updated scoping document. The initial human health risk assessment for cyflumetofen was conducted in 2014 (D. Wilbur, D398246, 07-JAN-2014). The most recent comprehensive human health risk assessment was completed in 2021 (A. Britt, D460045, 28-OCT-2021).

Cyflumetofen (2-methoxyethyl α-cyano-α-[4-(1,1-dimethylethyl)phenyl]-β-oxo-2-(trifluoromethyl)benzenepropanoate) is a miticidal active ingredient from BASF currently registered on a variety of crops including citrus fruit, grapes, pome fruit, strawberries, tomatoes, tree nuts, stone fruit, cucumber, hops and ornamental plants. Tolerances are established for cyflumetofen in/on the above plant commodities under 40CFR §180.677(a)(1) and are summarized in Appendix E. There are no tolerances established for cyflumetofen residues in livestock commodities.

HED has reviewed recent assessments and the existing database for cyflumetofen to determine the need for additional data and any updates to the human health risk assessment to support the forthcoming registration review decision. HED considered the most recent human health risk assessments with respect to cyflumetofen's toxicity, exposure, and use, the most updated Agency science policy and risk assessment methodologies, incident databases, and conducted a screening-level literature search (see Appendix A) to determine the scope of work necessary to support the registration review.

ANTICIPATED DATA NEEDS FOR CYFLUMETOFEN

Hazard: At the time of this scoping document, the hazard database for cyflumetofen was screened. No outstanding hazard data gaps have been identified. The need for a subchronic inhalation toxicity study was considered by the Hazard and Science Advisory Council (HASPOC) of HED, which recommended that the subchronic inhalation toxicity study was not required at that time (J. Van Alstine, TXR 0056691, 03-JUL-2013). This recommendation is still valid at this time.

As part of scoping for cyflumetofen registration review an open literature search was also conducted; see Appendix A. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned nine studies from the literature. During title/abstract screening of these studies, one study was identified as containing potentially relevant quantitative information for the cyflumetofen human health risk assessment. Following a full text review of the identified relevant study it was determined that it does not contain information that would impact the risk assessment. Rather, the results of this study concurred with the 90-day oral rat study already within the toxicology database for cyflumetofen (MRID 48542682).

Residue Chemistry: The residue chemistry database for cyflumetofen was screened and there were no outstanding residue chemistry data gaps. The residue of concern for tolerance enforcement and risk assessment in currently registered primary crops is parent cyflumetofen. The HED Residues of Concern Knowledgebase Sub-committee (ROCKS) considered the available data on the nature and magnitude of residues of cyflumetofen and concluded that if new uses on small grains, leafy vegetables and root/tuber crops are proposed in the future, additional metabolism studies may be required to determine the residues of concern (I. Negrón-Encarnación, D408530, 26-MAR-2013). There is no reasonable expectation of finite residues in livestock, so the ROCKS had no recommendation on residues of concern in livestock. The residues of concern for drinking water (risk assessment only) are the parent cyflumetofen and a subset of cyflumetofen degradates called AB degradates. The AB prefix refers to the phenyl (A) and tolyl (B) ring structures retained during degradation. They include AB-1, AB-7, AB-11, AB-12, AB-15, and the dimers AB-1, AU16 and AU17. Adequate nature of the residue, storage stability, rotational crop, and magnitude of the residue (plants and livestock) studies are available to support the registrations and tolerances. Validated analytical methods are available to enforce tolerances.

Based on communication with Craig Vigo (Analytical Chemistry Branch - Biological and Economic Analysis Division; 28-APR-2023), the analytical reference standard for cyflumetofen is current with an expiration of 01-OCT-2025.

Occupational/Residential Exposure: Since a dermal point of departure (POD) was not selected for cyflumetofen, dislodgeable foliar residue (DFR) studies are not needed for cyflumetofen at this time. If the PODs change, the need for DFR studies may be re-evaluated in the future to refine the occupational post-application assessment. All registered and proposed cyflumetofen labels require that residential handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use personal protective equipment (PPE) (e.g., gloves). Therefore, HED has made the assumption that these products are not for homeowner use, and a quantitative residential handler assessment is not needed at this time. Residential post-application exposures are expected to be negligible and there is no dermal endpoint for cyflumetofen.

RISK SUMMARY FOR CYFLUMETOFEN

Hazard Profile: The major target organ of cyflumetofen is the adrenal gland in rats, mice, and dogs following short-term and long-term oral exposure characterized by increased organ weight and histopathology (vacuolation and hypertrophy of the adrenal cortical cells). There is no evidence of neurotoxicity or immunotoxicity in any of the submitted studies for cyflumetofen.

There is no evidence of increased qualitative or quantitative susceptibility in the rat 2-generation reproduction study; however, the rat and rabbit developmental studies indicate susceptibility in the pups. There is evidence of increased quantitative susceptibility in the rabbit developmental toxicity study, since developmental effects (change in ossification, paw flexion, and decreased fetal body weight) were observed at the limit dose where no maternal toxicity was present. There is evidence of increased qualitative susceptibility in the rat developmental toxicity study as developmental effects (increased incidence of incompletely ossified sternal centra) were seen at the same dose that caused an increase in adrenal weights and organ-to-body weight ratio in the maternal animals.

Notwithstanding, the degree of concern for these effects in infants and children is low because the rat and rabbit developmental effects have clearly defined no observed adverse effect level (NOAEL)/ lowest observed adverse effect level (LOAEL) and the endpoints selected for risk assessment are protective of these effects. In addition, highly conservative exposure estimates were incorporated into the risk assessment. Taken together, these factors support the reduction of the Food Quality Protection Act (FQPA) safety factor to 1X. The previously selected points of departure (PODs) and toxicity endpoints are described in Appendix C.

Cyflumetofen has low acute toxicity by oral, dermal, and inhalation routes of exposure. It is irritating to the eyes, but not to the skin. Cyflumetofen is classified as Toxicity Category III via the oral route; Toxicity Category IV via the dermal and inhalation route; Toxicity Category II for eye irritation; and Toxicity Category IV for skin irritation potential. It is a skin sensitizer. Cyflumetofen has been classified as having "Suggestive Evidence of Carcinogenic Potential" based on the presence of a single tumor type (thyroid c-cell) in one sex (male) and one species (rat), and no concern for mutagenicity for the parent or the metabolites. The Agency has determined that quantification of risk using a non-linear approach (i.e., the chronic reference dose) will adequately protect for all chronic toxicity, including carcinogenicity, likely to result from exposure to cyflumetofen (K. Rury, TXR# 0056862, 30-Dec-2013).

In developing the incidents and epidemiology Tier 1 scoping assessment (S. Recore, D466977, 22-MAR-2023) for cyflumetofen, HED examined available incident and epidemiology data. HED queried the EPA Incident Data System (IDS), from January 1, 2018, to February 14, 2023, and found two incidents reported to Main IDS and one incident reported to Aggregate IDS that involved the active ingredient cyflumetofen. One incident reported to Main IDS was classified as moderate severity and the other was classified as minor severity. The incident reported to Aggregate IDS was classified as minor severity. HED also examined the National Institute of Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides database. A query of SENSOR-Pesticides from 1998-2017 identified no cases involving cyflumetofen.

HED also reviewed the Agricultural Health Study (AHS) publications listed on the AHS publication website and the open literature. As of January 2023, there were no epidemiological publications reporting on the potential association between cyflumetofen exposure and health effects. The Agency will continue to monitor the incident and epidemiological information through Registration Review.

Dietary Risk: An acute dietary risk assessment is not required since no endpoint attributable to a single oral exposure was identified from the available toxicity database. The most recent cyflumetofen chronic dietary risk assessment (S. Piper, D461525, 28-OCT-2021) resulted in risk estimates below HED's level of concern (LOC). The chronic dietary exposure estimate to the general U.S. population is 1% of the chronic population adjusted dose (cPAD) and to children 1-2 years old, the most highly exposed population subgroup, is 2.7% of the cPAD. Cyflumetofen is classified as "Suggestive Evidence of Carcinogenic Potential". The Agency determined that quantification of risk using a non-linear approach (i.e., the chronic reference dose) will adequately protect for all chronic toxicity, including carcinogenicity, likely to result from exposure to cyflumetofen (K. Rury, TXR 0056862, 30-Dec-2013). Therefore, a separate cancer assessment was not conducted, and the chronic exposure assessment is considered protective of any cancer exposures.

Residential Risk: All registered and proposed cyflumetofen labels require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use personal PPE (e.g., gloves). Therefore, HED has made the assumption that these products are not for homeowner use, and a quantitative residential handler assessment was not conducted. HED notes that there are registered uses of cyflumetofen to commercially treat garden vegetables that could be subsequently purchased at a retail location for transplant into a residential setting and treated ornamental plants that can be purchased by consumers. HED considers post-application exposure resulting from this scenario to be negligible because residues are expected to decline significantly from the time of application in a commercial setting to consumer purchase at a retail location. In addition to the negligible exposure potential, there is also no dermal hazard for cyflumetofen. Therefore, a quantitative residential post-application dermal risk assessment is not required since only adult exposures are expected, and children's incidental oral exposures are not expected from retail transplant in residential areas. Based on the registered uses and labels, residential assessments are not required at this time (A. Britt, D460045, 28-OCT-2021).

Acute Aggregate Risk: No toxic effects attributable to a single dose of cyflumetofen were observed in the toxicology database; therefore, a quantitative acute aggregate risk assessment for this chemical is not required.

Short- and Intermediate-Term Aggregate Risks: No residential scenarios were considered for inclusion in the short-term aggregate risk assessment.

Chronic Aggregate Risks: As there are no long-term residential exposures, the chronic aggregate risk estimates are equivalent to the chronic dietary risk estimates and result in no risks of concern. The chronic dietary exposure estimates to the general U.S. population is 1% of the cPAD and children 1-2 years old, the most highly exposed population subgroup, is 2.7% of the cPAD.

Cancer Aggregate Risks: A cancer aggregate assessment was not conducted since cyflumetofen is classified as "Suggestive Evidence of Carcinogenic Potential" and a non-linear approach will adequately account for all chronic toxicity, including carcinogenicity.

Occupational Risk: In the most recent risk assessment, an occupational handler exposure and risk assessment was conducted for the proposed amended uses of cyflumetofen on citrus fruits and tree nuts. The occupational handler risk estimates resulted in no risk estimates of concern [i.e., the estimated Margins of Exposure (MOEs) are ≥ the level of concern (LOC) of 100)] with label-required baseline attire (i.e., long-sleeved shirt, long pants, shoes and socks); the MOEs range from 32,000 to 5,800,000 (A. Britt, D464571, 14-JUN-2022). All occupational handler exposures were assessed for all currently registered uses and no risks of concern were identified (i.e., the MOEs are ≥ the LOC of 100). Based on the registered uses and labels, an occupational handler assessment is not required at this time.

In the most recent risk assessment, a quantitative occupational post-application exposure and risk assessment was not conducted for the proposed amended uses of cyflumetofen on citrus fruits and tree nuts because no dermal endpoint was selected (A. Britt, D464571, 14-JUN-2022). A quantitative occupational post-application exposure and risk assessment was not conducted for all currently registered uses because no dermal endpoint was selected for cyflumetofen.

Cumulative Risk: Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to cyflumetofen and any other substances and cyflumetofen does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that cyflumetofen has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[1] and conducting cumulative risk assessments (CRA)[2].

Cyflumetofen is an acaricide beta-ketonitrile. As part of the ongoing process to review registered pesticides, the Agency intends to apply this framework to determine if the available toxicological data for cyflumetofen suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

Endocrine Disruptor Screening Program (EDSP): Please see Appendix D for a discussion of the endocrine disruptor screening program as it relates to cyflumetofen.

ANTICIPATED RISK ASSESSMENTS FOR CYFLUMETOFEN FOR REGISTRATION REVIEW

As part of Registration Review, HED will evaluate the hazard database of cyflumetofen including endpoints, PODs, and FQPA uncertainty factors (FQPA UF) and safety factors (UF/ SF) consistent with current policies and practices.

A new chronic dietary risk assessment may be required which utilizes the most current version of the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID; version 4.02). Any revisions to the dietary assessment will incorporate up to date percent crop treated (PCT) data, monitoring data, any updated Estimated Drinking Water Concentration estimates from the Ecological Fate and Effects Division (EFED), and/or any revised toxicological PODs, as appropriate. Additionally, HED will consider the need to update tolerances, such as to reflect updated policies or harmonization, including consideration of any comments from stakeholders. Revisions to the current tolerances may be required to conform to current guidance concerning the tolerance expression, significant figures, commodity definition, crop group conversions, and/or for purposes of harmonization.

Updated occupational and residential assessment will be considered during registration review for cyflumetofen. Any updates to policies or practices for occupational or residential exposure and risk

[1] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)

[2] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

assessment will be incorporated at the time of the draft risk assessment for registration review, including updated PODs, exposure data (i.e., DFR), and the consideration of spray drift and volatilization for non-occupational bystanders.

REFERENCES

Previous Risk Assessments

Britt, A. 14-JUN-2022, D464571, "Cyflumetofen. Human Health Risk Assessment for the Proposed Amended Registration of Cyflumetofen on Citrus Fruit Crop Group 10-10A and Tree Nut Crop Group 14-12".

Britt, A. 28-OCT-2021, D460045, "Cyflumetofen. Human Health Risk Assessment for the Section 3 Registration Action for a New Use on Hops".

Wilbur, D., 07-JAN-2014, D398246, "Cyflumetofen. New Active Ingredient Human Health Risk Assessment to Support Uses on Citrus (Group 10-10), Pome Fruits (Crop Group 11-10, Tree Nuts (Crop Group 14-12), Grape, Strawberry, and Tomato."

Piper, S., 04-MAR-2019, D442300, "Cyflumetofen. Human Health Risk Assessment to Support New Uses on Imported Tea."

Piper, S., 16-SEP-2019, D448658, "Cyflumetofen. Human Health Risk Assessment to Support New Uses without U.S. Registration in/on Imported Coffee."

Shelat, S., 29-APR-2020, D450939, "Cyflumetofen. Human Health Risk Assessment for the Section 3 Registration Action for New Uses on Fruiting Vegetable (Crop Group 8-10), Stone Fruits (Crop Group 12-12), and Greenhouse Uses on Fruiting Vegetable, Cucumber, and Strawberry."

Britt, A., 28-OCT-2021, D460045, "Cyflumetofen. Human Health Risk Assessment for the Section 3 Registration Action for a New Use on Hops."

Residue Chemistry Chapter

Piper, S., 28-OCT-2021, D461526, "Cyflumetofen. Petition for the Establishment of Permanent Tolerances and Registration for Use on Hops. Summary of Analytical Chemistry and Residue Data."

Incident Report

Recore, S., 22-MAR-2023, D466977, "Cyflumetofen: Tier I (Scoping) Review of Human Incidents and Epidemiology."

Dietary Exposure Assessment

Piper, S., 28-OCT-2021, D461525, "Cyflumetofen. Chronic Aggregate Dietary Exposure and Risk Assessment for New Uses on Hops."

Occupational/Residential Exposure Assessment

Britt, A., 28-OCT-2021, D461738, "Cyflumetofen. Occupational and Residential Exposure Assessment for a Proposed Use on Hops."

Drinking Water Memorandum

Gardner, W., 17-MAY-2021, D460046, "Cyflumetofen: Drinking Water Exposure Assessment for a Proposed Section 3 New Use on Hops."

CARC Memorandum

Rury, K., 30-DEC-2013, TXR 0056862, "Cyflumetofen: Report of the Cancer Assessment Review Committee."

HASPOC Memorandum

Van Alstine, J., 03-JUL-2013, TXR 0056691, "Cyflumetofen: Summary of the Hazard and Science Policy Council (HASPOC) Meeting of June 6, 2013: Recommendations on the Need for an Inhalation Study."

ROCKS Memorandum

Negrón-Encarnación, I., 26-MAR-2013, D408530, "Cyflumetofen. Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS)."

Open Literature Studies (outside of tox profile table studies)

Yoshida, T. et al. "A repeated dose 90-day oral toxicity study of Cyflumetofen, a novel acaricide, in rats." The Journal of Toxicological Sciences 37.1 (2012): 91-104. https://doi.org/10.2131/jts.37.91

APPENDIX A. Summary of Literature Search

Table A.1. Search Criteria for Screening-level Literature Search.

Date and Time of Search: 01/17/2022; 02:10 pm
Search Details:
((Cyflumetofen)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

Studies Identified in PubMed*: **9**
SWIFT-Review** Tags:
7 for Animal
6 for Human
0 for NO TAG

All studies identified in the PubMed search were screened when the citation list was ≤100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the "Animal" and/or "Human" tag.

Number of Articles Identified as Relevant for Risk Assessment: **1**
Citations of Articles Identified as Relevant for Risk Assessment:
Yoshida, T. et al. "A repeated dose 90-day oral toxicity study of Cyflumetofen, a novel acaricide, in rats." The Journal of Toxicological Sciences 37.1 (2012): 91-104.

Conclusion of Literature Search: Following a full text review, no studies were identified that contained relevant information (either quantitative or qualitative) that would impact the risk assessment or that would be considered in the selection of Points of Departure (PODs) for the cyflumetofen human health registration review risk assessment. The results of the reviewed study (Yoshida et al. 2012) directly concurred with an existing study within the cyflumetofen toxicity database (MRID 48542682).

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.
**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize studies identified in the PubMed search based on the model of interest in the study (e.g. human, animal, *in vitro*, etc.).
Studies could have resulted in multiple tags which would account for citations identified in PubMed not matching the number of tagged citations."

APPENDIX B. Toxicology Data Requirements Summary Table for Cyflumetofen

The requirements (40CFR §158.500) for the food use of cyflumetofen are in Table B.1.

Table B.1. Toxicology Data Requirements for Cyflumetofen

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (non-rodent)	yes	yes
870.3200 21/28-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	yes	waived[a]
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (non-rodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (non-rodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation (bacterial)	yes	yes
870.5300 Mutagenicity—Gene Mutation (mammalian)	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395 Mutagenicity—Other Genotoxic Effects	yes	yes
870.5500 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	no
870.6100b 90-Day Neurotoxicity (hen)	no	no
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Developmental Neurotoxicity	no	no
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	yes
870.7800 Immunotoxicity	yes	yes

[a] HASPOC recommended the subchronic inhalation study is not needed (J. Van Alstine, TXR 0056691, 03-JULI-2013).

APPENDIX C. Endpoint Summary Table for Cyflumetofen

Table C.1. Summary of Toxicological Doses and Endpoints for Cyflumetofen for Use in Dietary, Non-Occupational and Occupational Human Health Risk Assessments*

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	An acute reference dose has not been established for either the general population or for females 13-49 years of age since there were no appropriate toxicological effects attributable to a single dose observed in available toxicity studies for either the general population or for females 13-49 years of age.			
Chronic Dietary (All Populations)	NOAEL= 16.5 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= 1X	cRfD = 0.17 mg/kg/day cPAD = 0.17 mg/kg/day	***Three co-critical studies*:** 90-day feeding study in rats MRID 48542682 LOAEL = 1000 ppm (54.5/62.8 mg/kg/day in M/F) based on hematology and organ weight changes in the liver, adrenal and kidney; and histopathology effects in the adrenals and the ovaries. NOAEL=300 ppm (16.5/19 mg/kg/day in males/females) Chronic toxicity/carcinogenicity study in rats MRID 48542696, 48542697 LOAEL = 1500 ppm (49.5/61.9 mg/kg/day in M/F) based on increased adrenal weights and histopathology of the adrenal cortex and uterine horn. NOAEL=500 ppm (16.5/20.3 mg/kg/day in males/females) Two generation reproduction study in rats MRID 48542702 Parental: LOAEL = 500 ppm (30.6/46.6 mg/kg/day in M/F) based on increased organ weight and histopathology in adrenals. NOAEL=150 ppm (9.2/13.8 mg/kg/day in males/females)
Adult Oral and child incidental oral (Short-and Intermediate-Term)	NOAEL = 16.5 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= 1X	LOC for MOE <100	***Same as chronic dietary endpoint***
Dermal (Short-, and Intermediate-Term)	No dermal hazard was identified. No appropriate endpoint was identified for risk assessment.			
Inhalation (Short-, and Intermediate-Term)	NOAEL = 16.5 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= 1X	Occupational and Residential LOC for MOE < 100	***Same as chronic dietary endpoint***

Table C.1. Summary of Toxicological Doses and Endpoints for Cyflumetofen for Use in Dietary, Non-Occupational and Occupational Human Health Risk Assessments*				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (oral, dermal, inhalation)	Cancer Classification: Suggestive Evidence of Carcinogenic Potential. (Rury, K., TXR# 0056862, 12/30/2013)			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

APPENDIX D. Endocrine Disruptor Screening Program

The Federal Food Drug and Cosmetic Act (FFDCA) §408(p) requires EPA to develop a screening program to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." (21 U.S.C. 346a(p)). In carrying out the Endocrine Disruptor Screening Program (EDSP), FFDCA section 408(p)(3) requires that EPA "provide for the testing of all pesticide chemicals," which includes "any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), including all active and pesticide inert ingredients of such pesticide." (21 U.S.C. 231(q)(1) and 346a(p)(3)). However, FFDCA section 408(p)(4) authorizes EPA to, by order, exempt a substance from the EDSP if the EPA "determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen." (21 U.S.C. 346a(p)(4)).

The EDSP initiatives developed by EPA in 1998 includes human and wildlife testing for estrogen, androgen, and thyroid pathway activity and employs a two-tiered approach. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid pathways. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship for any adverse estrogen, androgen, or thyroid effect. If EPA finds, based on that data, that the pesticide has an adverse endocrine effect on humans, FFDCA § 408(p)(6) also requires EPA, "… as appropriate, [to] take action under such statutory authority as is available to the Administrator … as is necessary to ensure the protection of public health." (21 U.S.C. 346a(p)(6))[3].

Between October 2009 and February 2010, EPA issued Tier 1 test orders/data call-ins (DCIs) for its first list of chemicals ("List 1 chemicals") for EDSP screening and subsequently required submission of EDSP Tier 1 data for a refined list of these chemicals. EPA received data for 52 List 1 chemicals (50 pesticide active ingredients and 2 inert ingredients). EPA scientists performed weight-of-evidence (WoE) analyses of the submitted EDSP Tier 1 data and other scientifically relevant information (OSRI) for potential interaction with the estrogen, androgen, and/or thyroid signaling pathways for humans and wildlife.[4]

In addition, for FIFRA registration, registration review, and tolerance-related purposes, EPA collects and reviews numerous studies to assess potential adverse outcomes, including potential outcomes to endocrine systems, from exposure to pesticide active ingredients. Although EPA has been collecting and reviewing such data, EPA has not been explicit about how its review of required and submitted data for these purposes also informs EPA's obligations and commitments under FFDCA section 408(p). Consequently, on October 27, 2023, EPA issued a Federal Register Notice (FRN) providing clarity on the applicability of these data to FFDCA section 408(p) requirements and near-term strategies for EPA to further its compliance with FFDCA section 408(p). This FRN, entitled *Endocrine Disruptor Screening Program (EDSP): Near-Term Strategies for Implementation' Notice of Availability and Request for*

[3] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.

[4] Summarized in *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions*; EPA-HQ-OPP-2023-0474-0001; https://www.regulations.gov/document/EPA-HQ-OPP-2023-0474-0001

Comment (88 FR 73841) is referred to here as EPA's EDSP Strategies Notice. EPA also published three documents supporting the strategies described in the Notice:

- *Use of Existing Mammalian Data to Address Data Needs and Decisions for Endocrine Disruptor Screening Program (EDSP) for Humans under FFDCA Section 408(p)*;
- *List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed;* and,
- *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions* (referred to here as List 1 Screening Conclusions).

The EDSP Strategies Notice and the support documents are available on www.regulations.gov in docket number EPA-HQ-OPP-2023-0474. As explained in these documents, EPA is prioritizing its screening for potential impacts to the estrogen, androgen, and thyroid systems in humans, focusing first on conventional active ingredients. Although EPA voluntarily expanded the scope of the EDSP to screening for potential impacts to the estrogen, androgen, and thyroid systems in wildlife, EPA announced that it is not addressing this discretionary component of the EDSP at this time, considering its current focus on developing a comprehensive, long-term approach to meeting its Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[5] and November 2022 ESA Workplan Update[6]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[7] indicate that available data were sufficient for FFDCA section 408(p) assessment and review for potential adverse effects to the estrogen, androgen, or thyroid pathways for wildlife. For the remaining 17 List 1 chemicals, Tier 1 WoE memoranda made recommendations for additional testing. EPA expects to further address these issues taking into account additional work being done in concert with researchers within the EPA's Office of Research and Development (ORD).

As discussed in EPA's EDSP Strategies Notice and supporting documents, EPA will be using all available data to determine whether additional data are needed to meet EPA's obligations and discretionary commitments under FFDCA section 408(p). For some conventional pesticide active ingredients, the toxicological databases may already provide sufficient evaluation of endocrine potential for estrogen, androgen, and/or thyroid pathways and EPA will generally not need to obtain any additional data to reevaluate those pathways, if in registration review, or to provide an initial evaluation for new active ingredient applications. For instance, EPA has endocrine-related data for numerous conventional pesticide active ingredients through either a two-generation reproduction toxicity study performed in accordance with the current guideline (referred to here as the updated two-generation reproduction toxicity study; OCSPP 870.3800 - Reproduction and Fertility Effects) or an extended one-generation reproductive toxicity (EOGRT) study (OECD Test Guideline 443 - Extended One-Generation Reproductive Toxicity Study). In these cases, EPA expects to make FFDCA 408(p)(6) decisions for humans without seeking further estrogen or androgen data. However, as also explained in the EPA's EDSP Strategies Notice, where these data do not exist, EPA will reevaluate the available data for the conventional active ingredient during registration review to determine what additional data, if any, might be needed to confirm EPA's assessment of the potential for impacts to estrogen, androgen,

[5] https://www.epa.gov/system/files/documents/2022-04/balancing-wildlife-protection-and-responsible-pesticide-use_final.pdf

[6] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf

[7] https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and

and/or thyroid pathways in humans. For more details on EPA's approach for assessing these endpoints, see EPA's EDSP Strategies Notice and related support documents.

Also described in the EPA's EDSP Strategies Notice is a framework that represents an initial approach by EPA to organize and prioritize the large number of conventional pesticides in registration review. For conventional pesticides with a two-generation reproduction toxicity study performed under a previous guideline (i.e., an updated two-generation reproduction toxicity study or an EOGRT is not available), EPA has used data from the Estrogen Receptor Pathway and/or Androgen Receptor Pathway Models to identify a group of chemicals with the highest priority for potential data collection (described in EPA's EDSP Strategies Notice as Group 1 active ingredients). For these cases, although EPA has not reevaluated the existing endocrine-related data, EPA has sought additional data and information in response to the issuance of EPA's EDSP Strategies Notice to better understand the positive findings in the ToxCast™ data for the Pathway Models and committed to issuing DCIs to require additional EDSP Tier 1 data to confirm the sufficiency of data to support EPA's assessment of potential adverse effects to the estrogen, androgen, and/or thyroid pathways in humans and to inform FFDCA 408(p) data decisions. For the remaining conventional pesticides (described in EPA's EDSP Strategies Notice as Group 2 and 3 conventional active ingredients), EPA committed to reevaluating the available data to determine what additional studies, if any, might be needed to confirm EPA's assessment of the potential for impacts to endocrine pathways in humans.

As noted in EPA's EDSP Strategies Notice and summarized above, where EPA has received endocrine-related data through an updated two-generation reproduction toxicity study or EOGRT study, EPA will generally not need to obtain any additional data, including EDSP Tier 1 data, to confirm its assessment of the potential for adverse effects to the estrogen and androgen pathways in humans. In the case of cyflumetofen, an updated two-generation reproduction toxicity study has been submitted and no additional data are needed, at this time, to support EPA's assessment of the potential for adverse estrogen and androgen effects in humans.

Several studies are available in the database for cyflumetofen that evaluated thyroid toxicity and there were no adverse thyroid effects observed related to thyroid hormone perturbations. No additional thyroid data are needed at this time. Therefore, EPA has concluded at this time that the points of departure for human health risk assessment to evaluate the EPA-registered uses and established tolerances of cyflumetofen are protective of potential adverse estrogen, androgen, and thyroid effects in humans. EPA will address its FFDCA section 408(p)(6) commitments and obligations as part of registration review.

APPENDIX E. List of Registered Uses/Use Sites for Cyflumetofen

General Tolerances for Cyflumetofen	
Commodity	**Parts per million**
Almond, hulls	4.0
Cherry subgroup 12-12A	1.5
Citrus, oil	16
Coffee, green bean [2]	0.08
Cucumber	0.3
Fruit, citrus, group 10-10	0.30
Fruit, pome, group 11-10	0.30
Grape	0.60
Hop, dried cones	30
Nut, tree, group 14-12	0.01
Peach subgroup 12-12B	0.4
Pepper/eggplant subgroup 8-10B	2
Plum subgroup 12-12C	0.3
Strawberry	0.6
Tea, dried [1]	40
Tomato subgroup 8-10A	0.7

[1] There are no U.S. registrations for this commodity as of May 8, 2019.
[2] There are no U.S. registrations for these commodities as of November 25, 2019.

Tolerances with Regional Registrations for Cyflumetofen

None.

Non-agricultural Use Sites for Cyflumetofen

	Non-Agricultural Use Site
1	Nursery ornamentals
2	Field-grown ornamental crops
3	Greenhouse ornamentals (roses, cut flowers)
4	Landscaping, trees/shrubs/bushes
5	Landscaping, plants/flowers
6	Interior landscaping

Residential Use Sites for Cyflumetofen

None.