Case No. 13-72346

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

POLLINATOR STEWARDSHIP COUNCIL, AMERICAN HONEY PRODUCERS ASSOCIATION, NATIONAL HONEY BEE ADVISORY BOARD, AMERICAN BEEKEEPING FEDERATION, THOMAS R. SMITH, BRET L. ADEE, and JEFFERY S. ANDERSON,

Petitioners,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY, *et al.*,

Respondents,

and

DOW AGROSCIENCES,

Respondent-Intervenor.

On Petition for Review of an Order of the
United States Environmental Protection Agency

PETITIONERS' EXCERPTS OF RECORD
VOLUME 1 of 3 (PAGES 1 – 254)

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Index to Petitioners' Excerpts of Record ("PER")

AR Doc.	Online Docket ID	Document Title	PER Page(s)
380	EPA-HQ-OPP-2010-0889-0342	Comment submitted by T. Smith	318-322
407	EPA-HQ-OPP-2010-0889-0369	Comment submitted by Bret Adee, President National Pollinator Defense Fund	323-335
420	EPA-HQ-OPP-2010-0889-0382	Exhibit 1 to comment submitted by Peter T. Jenkins: Caldrone, N. *Insect Pollinated Crops, Insect Pollinators and US Agriculture: Trend Analysis of Aggregate Data for the Period 1992-2009*.	336-362
420	EPA-HQ-OPP-2010-0889-0382	Exhibit 5 to comment submitted by Peter T. Jenkins: Cutler, P., et al. *Investigating the mode of action of sulfoxaflor: a fourth-generation neonicotinoid*.	363-375
422	EPA-HQ-OPP-2010-0889-0384	Comment submitted by Nichelle Harriott, Beyond Pesticides et al.	376-387
Volume 3			
N/A*	N/A*	U.S. EPA. 2012. White Paper in Support of the Proposed Risk Assessment Process for Bees.	388-662

* EPA considers the "White Paper in Support of the Proposed Risk Assessment Process for Bees" to be part of the administrative record, because it is listed as a reference in the "Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration" (AR Doc. 17). *See* PER 149.

vii. Explain your views as clearly as possible, avoiding the use of profanity or personal threats.

viii. Make sure to submit your comments by the comment period deadline identified.

3. *Environmental justice.* EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of any group, including minority and/or low-income populations, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical or disproportionately high and adverse human health impacts or environmental effects from exposure to the pesticides discussed in this document, compared to the general population.

II. What action is the agency taking?

EPA is announcing its receipt of several pesticide petitions filed under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a, proposing the establishment or modification of regulations in 40 CFR part 174 or part 180 for residues of pesticide chemicals in or on various food commodities. EPA has determined that the pesticide petitions described in this notice contain the data or information prescribed in FFDCA section 408(d)(2); however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data support granting of the pesticide petitions. Additional data may be needed before EPA can make a final determination on these pesticide petitions.

Pursuant to 40 CFR 180.7(f), a summary of each of the petitions that are the subject of this notice, prepared by the petitioner, is included in a docket EPA has created for each rulemaking. The docket for each of the petitions is available on-line at *http://www.regulations.gov.*

As specified in FFDCA section 408(d)(3), (21 U.S.C. 346a(d)(3)), EPA is publishing notice of the petition so that the public has an opportunity to comment on this request for the establishment or modification of regulations for residues of pesticides in or on food commodities. Further information on the petition may be obtained through the petition summary referenced in this unit.

New Tolerance

PP 9E7517. (EPA–HQ–OPP–2005–0477). Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268, proposes to establish a permanent tolerance in 40 CFR part 180 for residues of the herbicide safener dichlormid, acetamide, 2,2-dichloro-*N,N*-di-2-propenyl- (CAS Reg. No. 37764–25–3) in or on corn, field, forage; corn, field, grain; corn, field, stover; corn, pop, grain; corn, pop, stover; corn, sweet, forage; corn, sweet, kernel plus cob with husks removed; and corn, sweet, stover at 0.05 parts per million (ppm). Dichlormid (R–25788) is an herbicide safener that is used in the Dow AgroSciences LLC, acetochlor product line that is used for the control of grasses and broadleaf weeds in field corn, pop corn and sweet corn. Currently, time-limited tolerances on corn commodities are established with an expiration/revocation date of December 31, 2010. An adequate enforcement method for residues of dichlormid in corn has been developed and validated by the Analytical Chemical Laboratory (ACL) of EPA. Analysis is carried out using gas chromatography (GC) with nitrogen selective thermionic detection. A revised method was resubmitted to the EPA on October 29, 1999. Contact: Susan Stanton, (703) 305–5218, e-mail address: *stanton.susan@epa.gov.*

New Tolerance Exemptions

1. *PP* 9E7654. (EPA–HQ–OPP–2010–1004). Thro GmbH, c/o Thor Specialties, Inc., Trumbull, CT 06611, proposes to establish an exemption from the requirement of a tolerance for residues of 5-chloro-2-methyl-4-isothiazolin-3-one (in combination with 2-methyl-4-isothiazolin-3-one) (CAS Reg. Nos. 26172–55–4 and 2682–20–4) under 40 CFR 180.910 and under 40 CFR 180.930 when used as an inert ingredient as an "in-can" materials preservative with a maximum concentration of 50 parts per million (ppm) in pesticide formulations. The petitioner believes no analytical method is needed because requirements for an analytical method are not applicable to a request to establish an exemption from the requirement of a tolerance. Contact: Kerry Leifer, (703) 308–8811; e-mail address: *leifer.kerry@epa.gov.*

2. *PP* 9F7653. (EPA–HQ–OPP–2010–1005). Thor GmbH, c/o Thor Specialties, Inc, Trumbull, CT 06611, proposes to establish an exemption from the requirement of a tolerance for residues of 2-methyl-4-isothiazolin-3-one (CAS Reg. No. 2682–20–4) under 40 CFR 180.910 and under 40 CFR 180.930 when used as an inert ingredient as an "in-can" materials preservative with a maximum concentration of 250 parts per million (ppm) in pesticide formulations. The petitioner believes no analytical method is needed because requirements for an analytical method are not applicable to a request to establish an exemption from the requirement of a tolerance. Contact: Kerry Leifer, (703) 308–8811; e-mail address: *leifer.kerry@epa.gov.*

3. *PP* 0E7811. (EPA–HQ–OPP–2007–1077). Whitmire Micro-Gen Research Laboratories, Inc., c/o Landis International, Inc., P.O. Box 5126, Valdosta, GA 31603–5126, proposes to establish an exemption from the requirement of a tolerance for residues of carbon dioxide (CAS Reg. No. 124–38–9) under 40 CFR 180.910 and under 40 CFR 180.930 when used as an inert ingredient as a propellant in pesticide formulations. The petitioner believes no analytical method is needed because requirements for an analytical method are not applicable to a request to establish an exemption from the requirement of a tolerance. Contact: Karen Samek, (703) 347–8825; e-mail address: *samek.karen@epa.gov.*

List of Subjects

Environmental protection, Agricultural commodities, Feed additives, Food additives, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: December 9, 2010.

Lois Rossi,

Director, Registration Division, Office of Pesticide Programs.

[FR Doc. 2010–31872 Filed 12–21–10; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPP–2010–0889; FRL–8856–8]

Pesticide Products; Registration Applications

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has received applications to register pesticide products containing active ingredients not included in any previously registered pesticide products. Pursuant to the provisions of section 3(c)(4) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA is hereby providing notice of receipt and opportunity to comment on these applications.

DATES: Comments must be received on or before January 21, 2011.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2010–0889, by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the on-line instructions for submitting comments.
- *Mail:* Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001.
- *Delivery:* OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket Facility's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305–5805.

Instructions: Direct your comments to docket ID number EPA–HQ–OPP–2010–0889. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at *http://www.regulations.gov,* including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The regulations.gov Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the docket index available at *http://www.regulations.gov.* Although listed in the index, some information is not publicly available, *e.g.,* CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov,* or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Kable Bo Davis, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 306–0415; e-mail address: *davis.kable@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. Potentially affected entities may include, but are not limited to:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT.**

B. What should I consider as I prepare my comments for EPA?

1. *Submitting CBI.* Do not submit this information to EPA through regulations.gov or e-mail. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD–ROM that you mail to EPA, mark the outside of the disk or CD–ROM as CBI and then identify electronically within the disk or CD–ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. *Tips for preparing your comments.* When submitting comments, remember to:

i. Identify the document by docket ID number and other identifying information (subject heading, **Federal Register** date and page number).

ii. Follow directions. The Agency may ask you to respond to specific questions or organize comments by referencing a Code of Federal Regulations (CFR) part or section number.

iii. Explain why you agree or disagree; suggest alternatives and substitute language for your requested changes.

iv. Describe any assumptions and provide any technical information and/or data that you used.

v. If you estimate potential costs or burdens, explain how you arrived at your estimate in sufficient detail to allow for it to be reproduced.

vi. Provide specific examples to illustrate your concerns and suggest alternatives.

vii. Explain your views as clearly as possible, avoiding the use of profanity or personal threats.

viii. Make sure to submit your comments by the comment period deadline identified.

II. Registration Applications

EPA has received applications to register pesticide products containing active ingredients not included in any previously registered pesticide products. Pursuant to the provisions of section 3(c)(4) of FIFRA, EPA is hereby providing notice of receipt and opportunity to comment on these applications. Notice of receipt of these applications does not imply a decision by the Agency on these applications.

File symbol: 62719–AGR. *Applicant:* Dow AgroSciences, 9330 Zionsville Rd., Indianapolis, IN 46268. *Product name:* Sulfoxaflor Technical. *Active ingredient:* Insecticide and sulfoxaflor at 97.9%. *Proposed classification/Use:* Food and nonfood uses on the following use sites: Barly, Brassica (cole) leafy vegetables, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables (except Brassica), leaves of root and

tuber vegetables, low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, root and tuber vegetables, small fruit vine climbing (except fuzzy kiwifruit), soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turfgrass, watercress and wheat. Contact: Kable Bo Davis, (703) 306–0415, *davis.kable@epa.gov.*

File symbol: 62719–AEL. *Applicant:* Dow AgroSciences, 9330 Zionsville Rd., Indianapolis, IN 46268. *Product name:* Transform WG. *Active ingredient:* Insecticide and sulfoxaflor at 50%. *Proposed classification/Use:* Food and nonfood uses on the following use sites: Barly, Brassica (cole) leafy vegetables, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables (except Brassica), leaves of root and tuber vegetables, low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, root and tuber vegetables, small fruit vine climbing (except fuzzy kiwifruit), soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turfgrass, watercress and wheat. Contact: Kable Bo Davis, (703) 306–0415, *davis.kable@epa.gov.*

File symbol: 62719–AEG. *Applicant:* Dow AgroSciences, 9330 Zionsville Rd., Indianapolis, IN 46268. *Product name:* GF–2032 SC. *Active ingredient:* Insecticide and sulfoxaflor at 21.8%. *Proposed classification/Use:* Food and nonfood uses on the following use sites: Barly, Brassica (cole) leafy vegetables, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables (except Brassica), leaves of root and tuber vegetables, low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, root and tuber vegetables, small fruit vine climbing (except fuzzy kiwifruit), soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turfgrass, watercress and wheat. Contact: Kable Bo Davis, (703) 306–0415, *davis.kable@epa.gov.*

List of Subjects

Environmental protection, Pesticides and pest.

Dated: December 9, 2010.

Lois Rossi,

Director, Registration Division, Office of Pesticide Programs.

[FR Doc. 2010–32033 Filed 12–21–10; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPP–2010–0854; FRL–8851–3]

Petition for Rulemaking To Establish Procedures Consistent With Section 1010 of the 1988 Amendments to the Endangered Species Act; Notice of Availability

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA is announcing the availability of a September 16, 2010 petition from Growers for ESA Transparency ("GET"). GET is a coalition of growers throughout the western United States. GET is committed to improving the consultation process for, the transparency of, and accessibility to the Endangered Species Act (ESA). GET is requesting EPA to take immediate action to establish, by rulemaking, clear and equitable procedures for notice and comment on the Agency's pesticide effects determinations for endangered species and subsequent actions, including draft biological opinions and potential product restrictions consistent with section 1010 of the 1988 amendments to the ESA. This petition is similar to the petition filed on January 19, 2010 by DOW AgroSciences LLC, Makhteshim Agan of North America, and Cheminova, Inc. USA requesting EPA to promulgate a rule for amending Endangered Species Protection Bulletins (EPA–HQ–OPP–2010–0474).

DATES: Comments must be received on or before February 22, 2011.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2010–0854, by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the on-line instructions for submitting comments.
- *Mail:* Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001.
- *Delivery:* OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket Facility's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305–5805.

Instructions: Direct your comments to docket ID number EPA–HQ–OPP–2010–0854. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at *http://www.regulations.gov,* including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The regulations.gov Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the docket index available at *http://www.regulations.gov.* Although listed in the index, some information is not publicly available, *e.g.,* CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov,* or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Catherine Eiden, Pesticide Re-evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 20 2012

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

SUBJECT: Review of Benefits for Sulfoxaflor for Fruiting Vegetables, Cucurbit Vegetables, Citrus, and Cotton. (DP# 384640)

FROM: Don Atwood, Entomologist
Biological Analysis Branch
Biological and Economic Analysis Division (7503P)

THRU: Arnet Jones, Chief
Biological Analysis Branch
Biological and Economic Analysis Division (7503P)

TO: Jennifer Urbanski, Chemical Review Manager
Insecticide-Rodenticide Branch
Registration Division (7505P)

Product Review Panel date: November 19, 2012

SUMMARY and CONCLUSIONS

Dow AgroSciences submitted an application for a Section 3 Registration for the new insecticide sulfoxaflor. BEAD has reviewed efficacy of alternative insecticides for four crop groups: fruiting vegetables, cucurbit vegetables, citrus, and cotton. Due to ongoing concerns for honey bees, the review also assesses the importance of commercial honey bees as crop pollinators for the assessed crop groups.

Based on submitted and readily available efficacy information, BEAD concludes that sulfoxaflor will play an important role in pest management on these crops. Due to its unique chemistry and lack of cross-resistance to the neonicotinoid class insecticides, sulfoxaflor should be a valuable tool in pesticide resistance management. Furthermore, while honey bees play an important role as pollinators in the crop groups examined, growers should be able to time the application of sulfoxaflor as to result in minimal exposure to honeybees.

INTRODUCTION AND BACKGROUND

Dow AgroSciences has submitted an application to the Registration Division (RD) of the Office Pesticide Programs Chemical Safety and Pollution Prevention of the EPA for a Section 3 registration of the insecticide sulfoxaflor for use on cotton, soybean, cereals, citrus, leafy and fruiting vegetables, grapes, cole crops, and apples. Sulfoxaflor has been registered for use on cotton in the mid-south production region under a Section 18 emergency exemption to control tarnished plant bug since 2012. Due to potential risks to honey bees, BEAD was requested by RD to conduct an assessment on four of the crop groups (fruiting vegetables, cucurbit vegetables, citrus, and cotton) to determine benefits which would be associated with the registration of sulfoxaflor. As part of this assessment BEAD also examines the importance of honey bees in the production of each of the assessed crop groups.

General Information About Sulfoxaflor

Sulfoxaflor (XDE-208) is a new insecticide which targets a broad spectrum of piercing/sucking insects including aphids, plant bugs, whiteflies, planthoppers, mealybugs, and scales. Sulfoxaflor is the first member of a new class of insecticides, the sulfoximines. The sulfoximines act through a unique interaction with the nicotinic acetylcholine receptor in insects. Similar to neonicotinoids, sulfoxaflor is a highly efficacious agonist of the nicotinic receptor with low affinity for the imidacloprid binding site. The structure of sulfoxaflor makes it stable in the presence of a monooxygenase enzyme that was shown to degrade a variety of neonicotinoids. This stability results in broad lack of cross-resistance to neonicotinoids and other insecticide families. Sulfoxaflor acts through both contact and ingestion and provides both knockdown and residual control.

Scope of the Assessment: Data used for this assessment consisted of USDA data (Agricultural Chemical Usage, Agricultural Statistics, Census of Agriculture, Crop Profiles, and Pest Management Strategic Plans), state insecticide recommendations, California Pesticide Use Reporting (CPUR), publically available documents/efficacy studies, and EPA proprietary

use/usage data. Insect pests were not considered in the assessment if the proposed labeling indicated that sulfoxaflor will only provide suppression rather than control.

BENEFIT ASSESSMENTS

Crop Production in the United States

Based on available crop acreage data in 2007 (USDA/NASS 2009), fruiting vegetables were grown on approximately 550,400 acres, cucurbit vegetables on 539,400 acres, citrus on 1,004,500 acres, and cotton on 10,493,200 acres. Table 1 provides the acreage for each available crop for the designated crop groups.

Table 1. Crop Production by Crop Group in the United States.

Crop Group	Crop	Acres in U.S.
Fruiting Vegetables and Okra	Eggplant	6,038
	Okra	2,444
	Peppers, Bell	62,363
	Peppers, Other	37,372
	Tomatoes	442,225
Cucurbit Vegetables	Cantaloupe	84,290
	Cucumbers	151,759
	Honeydew Melons	13,573
	Pumpkins	92,955
	Squash	54,454
	Watermelons	142,359
Citrus	Grapefruit	102,578
	Lemons	66,972
	Limes	1,251
	Oranges	785,856
	Tangelos	9,694
	Tangerines	36,965
	Temples	1,211
Cotton	Cotton	10,493,238

Source: USDA/NASS 2007 Census of Agriculture

Cotton production accounts for 83.4 % of the total acreage which could potentially be treated with sulfoxaflor. Based on acres produced information, the assessment will be directed towards the following representative crops for each crop group; fruiting vegetables (tomatoes and pepper), cucurbit vegetables (watermelons, cucumbers, pumpkins, cantaloupe, and squash), citrus (oranges and grapefruit), and cotton.

Fruiting Vegetables

Limitations for Fruiting Vegetables: This analysis is limited to insecticide use on tomatoes and peppers. These crops were chosen as they represent most acreage in the fruiting vegetable crop group.

Label Pest(s): Aphids, plant bugs, greenhouse whitefly (outdoors), silverleaf whitefly, sweetpotato whitefly, thrips (suppression only)

Primary Production States: Peppers (Florida, New Mexico, and California) and Tomatoes (Florida and California)

Registered Alternatives: Registered alternatives for the labeled pests are presented in Table 2.

Registrant's Justification: The efficacy of registered alternatives for target pest control in fruiting vegetables was reviewed by the registrant and the benefits claimed by the registrant are:

1. Aphids - Heavy aphid infestations may cause wilting of tomato, but damage does not usually result in yield loss. Of greater significance, however, is that aphids vector tomato diseases such as alfalfa mosaic and tomato yellow top.
2. Whitefly - Whiteflies damage fruiting vegetables, tomatoes in particular, by sucking plant juices from the undersides of leaves causing them to turn yellow and die. The honeydew excreted from feeding activity glazes the plant surfaces and permits development of sooty mold on the surface. The fungus often retards growth and reduces the market value of the fruit. More importantly, whiteflies vector destructive Gemini viruses such as Tomato mottle and Tomato yellow leaf curl virus, which can and have resulted in total crop failure.
3. Aphids and whiteflies have developed resistance to a number of insecticides, including carbamates, neonicotinoids, organophosphates, and pyrethroids. Importantly for whiteflies, insecticide efficacy varies against adult and immature stages. More insecticide options are needed to continue to maintain viable insecticide options to integrate in a comprehensive insecticide resistance management (IRM) program and to extend the functional life of all insecticides.
4. Sulfoxaflor would provide an excellent rotation partner because it is highly effective against aphids and whiteflies and offers a novel mode of action to manage resistance development.
5. Sulfoxaflor provided control of all aphid species greater than or equal to control provided by acetamiprid, imidacloprid, and spirotetramat applied at normal use rates.
6. Sulfoxaflor provides whitefly control equivalent to pyriproxyfen+spirotetramat, imidacloprid, and dinotefuran.

BEAD's Response: Despite the numerous options potentially available, many producers are dependent on insecticides for suppression of aphids (Green peach and Potato) and whiteflies (Greenhouse, Silverleaf, and Sweet potato). BEAD agrees that while aphid feeding does not result in substantial crop losses, they are potential vectors of viral diseases. BEAD also agrees that whitefly control is necessary to prevent vectoring of viruses which can result in complete crop loss.

1. Aphids - Chemical control is advised for both green peach and potato aphid when action thresholds of 3-4 aphids per terminal three leaflets or 50% of leaves are infested (Webb et.al., 2010). Early in the season, aphid infestations are often spotty, and if such plants or areas are treated in a timely manner, great damage can be prevented later in the season (University of Florida, 2005).

a. Potato aphid - The potato aphid is primarily a pest in the Northeast and is generally the easiest to control. Effective insecticide active ingredients include: organophosphates such as acephate and dimethoate; carbamates such as oxamyl and methomyl; pyrethroids; neonicotinoids such as imidacloprid, thiamethoxam, dinotefuran, and acetamiprid; and several novel homopteran-specific and IPM-friendly insecticides such as pymetrozine, spirotetramat and flonicamid. (VCE 2009)
b. Green peach aphid -In some cases, use of insecticides for other, more damaging insects sometimes leads to outbreaks of green peach aphid. Inadvertent destruction of beneficial insects is purported to explain this phenomenon, but aphid resistance to some types of insecticide may also be involved. In addition, Cutler et. al. (2009) determined that sublethal exposure to imidacloprid and azadirachtin can induce hormetic responses, increased reproduction, in green leaf aphid. Application of insecticides rarely is effective in managing the viruses transmitted by aphids, rather insecticides simply slow the spread of disease.

2. Whiteflies - Chemical control of whiteflies in tomato and pepper production is advised when scouting determines 0.5 pupae or nymphs per leaflet or 10 adults per plant (0-3 true leaves) or 1 adult per leaflet (over 3 true leaves) (Webb et.al., 2012). Thresholds have not yet been established for greenhouse whitefly. Failure to control high populations of whiteflies can result in stunting, defoliation, and reduced (Florida IPM, 2012) yields. Drenches of systemic neonicotinoid insecticides such as imidacloprid, thiamethoxam, and dinotefuran before and immediately following transplanting provide early season control that is essential for most tomato production (Florida IPM, 2012). Neonicotinoid drenches provide protection for 6-8 weeks. It is important to alternate different modes of action and not use neonicotinoid insecticides back to back to prevent development of resistant populations (Florida IPM, 2012). While systemic neonicotinoids, primarily imidacloprid, currently provide the bulk of early season control of both whiteflies and aphids and can provide late season control as foliar applications, their continued use after the initial a-planting application is discouraged (Florida IPM, 2012). It is recommended that alternative insecticides be used when the initial at-plant neonicotinoid applications loose effectiveness to prevent development of resistant populations and thereby maintain the effectiveness of the systemic neonicotinoids. While numerous alternative insecticides can provide mid-season control of aphid and whitefly nymphs, endosulfan has been primarily recommended for late season adult whitefly control (Atwood and Rim, 2009). However, endosulfan will no longer be available for use on fruiting vegetables in Florida after December 31, 2014 and in other states after July 15, 2015 (EPA, 2010). Sulfoxaflor could serve as a replacement for the loss of endosulfan for control of mid-season whitefly, particularly in relation to its lack of cross-resistance to neonicotinoid insecticides.
3. Green peach aphid exhibits a striking capacity for rapid adaptation to insecticides, developing resistance to more active compounds than any other known insect (Vasquez, 1995), Six distinct insecticide resistance mechanisms mediating different levels of insensitivity, have been described for the species: (i) Modified acetylcholinesterase (MACE), which confers resistance to organophosphates and carbamate insecticides, (ii) kdr, kinase insert domain receptor), and super kdr mutations in a voltage-gated sodium channel, which is the target of pyrethroids and organochlorines, (iii) the mutation of the

GABA receptor, rdl, which is target of organochlorines of the cyclodiene type, (iv) the recently described mutation of a key residue in the loop D region of a nAChR b1 subunit, (v) the overproduction of esterases E4 or FE4 confers resistance to organophosphates, pyrethroids and to a lesser extent carbamates, and (vi) the recently described over-production of a cytochrome P450 confers resistance to neonicotinoids (Silva et. al. 2012).

4. As shown in Table 2, no insecticides other than neonicotinoids are rated as providing excellent control of either aphids or whiteflies on fruiting vegetables. BEAD agrees that sulfoxaflor has a novel mode of action, with no cross-resistance to neonicotinoids, which could be effective against aphids and whiteflies and also maintain the viability of currently registered insecticides when used in a rotational insecticide resistance management (IRM) program. The lack of cross-resistance would make sulfoxaflor a useful alternative in programs such as Florida tomato production which currently limit highly effective neonicotinoids to either at-plant application or mid- to late-season foliar application to manage neonicotinoid pesticide resistance.
5. While the registrant does provide studies showing the effectiveness of sulfoxaflor against aphid pests on vegetables, the registrant failed to provide data specific for fruiting vegetables. BEAD cannot fully assess the efficacy of sulfoxaflor for this crop group based on the data provided. However, based on studies conducted on other crop groups and identical pests, BEAD has no reason to believe that sulfoxaflor would not be equally effective against aphids on fruiting vegetables.
6. The registrant does provide studies, on tomatoes, that indicate sulfoxaflor can provide effective control of whiteflies on fruiting vegetables. However, of the insecticides used in their comparison tests, only imidacloprid and spirotetramat are currently used on greater than 5% of total acreage (Table 1). In addition, imidacloprid is primarily used as an at-plant application. Therefore, it is not possible for BEAD to conclude that sulfoxaflor will be equally efficacious as the currently used foliar insecticides for whitefly control in fruiting vegetables. However, due to the lack of cross-resistance with neonicotinoids and the exhibited effectiveness of foliar imidacloprid application, sulfoxaflor should be an effective alternative for use against mid- and late-season whitefly populations.

Table 2. Market leader insecticides for pest control on fruiting vegetables.

Pest[1]	Insecticide[2]	Crop Acres Treated (%)[3,4,5,5]	Efficacy Rating for Representative Crops[6]							
			Tomato				Pepper			
			CA[7, 8,9,10]	SC GA[11]	VA NC DE[12, 13]	FL[14, 15]	CA[16, 17,18] and NM[19]	DE MD NJ[20]	OH_{21}	GA SC[22]
Aphids (Green peach and Potato)	Azadirachtin	5.8	-	-		R	P			
	Bifenthrin	6.2	-	-		R				
	Dimethoate	17.6	G	-	R	R	P-F	F	G	
	Imidacloprid	21.5	G	E	R	R	G-E	G	G	E
	Methomyl	7.9	G	-		R	F-G	F	G	
	Thiamethoxam	5.8	-	-	R	R	G-E	G	G	
Whitefly (Greenhouse, Silverleaf, and Sweet potato)	Azadirachtin	11.8	-			P	P			
	Bifenthrin	11.0	-	F-G		P				F-G
	Chlorantraniliprole	11.0	-							
	Imidacloprid	19.0	E	G-E	R	F-E	G-E		G	F-E
	Oxamyl	6.0	F	F-G		P-F				F-G
	Spirotetramat	6.4	-							

1 Plant bugs were not included as proprietary data indicates no insecticide usage against this pest. Does not include pests where control is limited to suppression (thrips).

2 Only includes alternatives which account for greater than 5 percent of treated acres

3 Does not reflect total crop treated. Based only on the crop acres treated for the specific pest

4 Adjusted to reflect cancellation of endosulfan

5 USEPA. 2012. Proprietary data for 2009 - 2011

6 Rating Scale: E=Excellent, G=Good, F=Fair, P=Poor, R=Recommended but no comparative efficacy ranking

7 USDA. 2003a. Pest Management Strategic Plan California Fresh Market Tomato Production.

8 UC IPM. 2008a. UC Pest Management Guidelines – Tomato – Green Peach and Other Early Season Aphids.

9 UC IPM. 2008b. UC Pest Management Guidelines – Tomato – Potato Aphid.

10 UC IPM. 2008c. UC Pest Management Guidelines – Tomato – Whiteflies.

11 USDA. 2007a. Pest Management Strategic Plan for Tomato in Georgia and South Carolina.

12 USDA. 2006a. Pest Management Strategic Plan for Tomato in Virginia, North Carolina, and Delaware.

13 VCE. 2009. Potato Aphids on Tomatoes. Virginia Cooperative Extension.

14 Webb, SE, PA Stansly, DJ Schuster and JE Funderburk. 2010. Insect Management for Tomatoes, Peppers, and Eggplant.

15 Schuster, DJ, PA Stansly, JE Polston, P Gilreath and E McAvoy. 2007. Management of Whiteflies, Whitefly-Vectored Plant Virus, and Insecticide Resistance for Vegetable Production in Southern Florida.

16 USDA. 2004. A Pest Management Strategic Plan for Pepper Production in California.

17 UC IPM. 2009a. UC Pest Management Guidelines – Peppers – Green Leaf Aphid.

18 UC IPM. 2009b. UC Pest Management Guidelines – Peppers – Whiteflies.

19 USDA. 2000. Crop Profile for Peppers (Chile) in New Mexico.

20 USDA. 2008b. Pest Management Strategic Plan for Bell and Non-Bell Peppers in Delaware, Eastern Shore Maryland, and New Jersey.

21 USDA. 2003b. Bell Pepper and Non-Bell Pepper Pest Management Strategic Plan.

22 USDA. 2007b. Pest Management Strategic Plan for Pepper in Georgia and South Carolina.

Cucurbit Vegetables

Limitations for Cucurbit Vegetables: This analysis is limited to insecticide use on watermelons, cucumbers, pumpkins, cantaloupe, and squash. These crops were chosen as they represent most acreage in the cucurbit vegetable crop group.

Pest(s): aphids, silverleaf whitefly, sweet potato whitefly, thrips (suppression only)

Registered Alternatives: Registered alternatives for the labeled pests are presented in Table 3.

Registrant's Justification: The registrant did not provide either a justification or benefit assessment specifically for cucurbit vegetables. However, the registrant did submit efficacy studies supporting the efficacy of sulfoxaflor on cucurbit crops.

BEAD's Response:

1. BEAD has assessed cucurbit vegetables based on the registrant-provided information on vegetables in general. As the primary pests targeted for control with sulfoxaflor are similar across all vegetable crop groups, aphid and whitefly, BEAD concludes that similar insecticide resistance occurs in cucurbit vegetables as noted for fruiting vegetables. For additional information, refer to the previous discussion of fruiting vegetables.
2. As shown in Table 3, and as determined for fruiting vegetables, the only market leader alternative insecticide which is rated as providing excellent control of aphid is imidacloprid. The only current market leader insecticides which are rated as providing excellent control of whitefly are imidacloprid and pymetrozine. BEAD agrees that sulfoxaflor has a novel mode of action, with no cross-resistance to neonicotinoids, which could be effective against aphids and whiteflies and also maintain the viability of currently registered insecticides when used in a rotational insecticide resistance management (IRM) program. The lack of cross-resistance would make sulfoxaflor a useful alternative in cucurbit production programs which currently limit highly effective neonicotinoids to either at-plant application or mid- to late-season foliar application to manage neonicotinoid pesticide resistance.
3. The registrant submitted three studies for sulfoxaflor on cantaloupe and one for summer squash. Comparison of imidacloprid and sulfoxaflor on summer squash to control cotton aphid indicates that sulfoxaflor is equivalent to imidacloprid at the two low application rates (15 and 25 g ai/ha) and superior to imidacloprid at the highest application rate (50 g ai/ha). The three efficacy studies for whitefly control on cantaloupe determined that sulfoxaflor provides control equivalent to both acetamiprid and spiromesifen.
4. Although the registrant did not provide a justification and benefit assessment for sulfoxaflor use on cucurbit vegetables, based on the field efficacy studies and the target pests, BEAD concludes that sulfoxaflor would provide an additional insecticide capable of providing excellent control of both aphids and whiteflies on cucurbits.

Table 3. Market leader insecticides for pest control on cucurbit vegetables.

Pest[1]	Insecticide[2]	Crop Acres Treated (%)[3,4,5]	Insecticide Efficacy[6]					
			FL water-Melon[7]	DE, MD, NJ, NC Water-Melon[8]	DE, MD pickling cucumber[9]	TN cucurbit[10]	CA melon[11]	IL, IN, IA, MI Pumpkin[12]
Aphids (Green peach and Melon)	Azadirachtin	11.8	F				P	P-F
	Bifenthrin	11.0	P	P-F		G	G	G
	Chlorantraniliprole	11.0						
	Imidacloprid	19.0	E	VG	G		E	G
	Oxamyl	6.0		NL-E		F	F	F
	Spirotetramat	6.4						
Whitefly (Silverleaf and Sweet potato)	Bifenthrin	22.8	F				F	F-G
	Chlorantraniliprole	6.0						
	Dinotefuran	15.2						
	Imidacloprid	21.8	E			E	E	N-P
	Pymetrozine	5.5	G			E		G
	Spiromesifen	6.6						

1 Does not include pests where control is limited to suppression (thrips).
2 Only includes alternatives which account for greater than 5 percent of treated acres
3 USEPA. 2012. Proprietary Data for 2009-2011.
4 Does not reflect total crop treated. Based only on the crop acres treated for the specific pest
5 Adjusted to reflect cancellation of endosulfan
6 Rating Scale: E=Excellent, VG= Very Good, G=Good, F=Fair, P=Poor, R=Recommended but no efficacy data, NL=Not labeled for pest, but effective
7 USDA. 2007c. Watermelon Pest Management Strategic Plan (PMSP).
8 USDA. 2008c. Pest Management Strategic Plan for Watermelons in Delaware, Maryland, New Jersey, and North Carolina.
9 USDA. 2005a. Pest Management Strategic Plan for Cucumbers (Pickling) in Delaware and Eastern Shore Maryland.
10 USDA. 2002a. Tennessee's Pest Management Strategic Plan for Cucurbits.
11 USDA. 2003c. Pest Management Strategic Plan Cantaloupe, Honeydew, and Mixed Melon Production in California.
12 USDA. 2005b. Midwest Pest Management Strategic Plan for Processing & Jack-o-Lantern Pumpkins Illinois, Indiana, Iowa and Missouri.

Benefits Assessment for Citrus

Limitations for Citrus: This analysis is limited to available usage data on orange, grapefruit, and lemon. Due to the majority of citrus production occurring in Florida and California, the benefit assessment for aphids, mealybugs, scales are primarily based on usage information for these states. The benefit assessment for psyllid is based on usage data for Texas and Florida.

Pest(s): – aphids, mealybugs, California red scale, citricola scale, citrus psyllid, citrus snow scale, thrips (suppression only)

Registered Alternatives: Registered alternatives for the labeled pests are presented in Table 4.

Registrant's Justification: The efficacy of registered alternatives for target pest control in citrus was reviewed by the registrant and the benefits claimed by the registrant are:

1. Aphids – No justification or benefits were included in the submission package.
2. Mealybugs – Mealybugs extract plant sap, reducing tree vigor, and excrete honeydew, which gets on plant surfaces and provides a surface upon which sooty mold grows. If a cluster of mealybugs feeds along a fruit stem, fruit drop can occur. Mealybugs are primarily managed by conserving their natural enemies and reducing ant populations and dust, however, economic populations of mealybugs do occur sporadically and require treatment. Chlorpyrifos is the primary insecticide used to control sporadic outbreaks of mealybugs on citrus.
3. Psyllid – Asian citrus psyllid was first observed in Florida in 1998. Once established, this exotic insect has become the most important insect pest of Florida citrus due to the presence of citrus greening disease, which is spread by the psyllid. The Asian citrus psyllid was first detected in California in 2008, but, fortunately, has not yet brought citrus greening disease to California. The California Department of Food and Agriculture has issued quarantines in several counties in an attempt to eradicate the pest before it becomes permanently established. Recommended insecticides for Asian citrus psyllid include chlorpyrifos, dimethoate, fenproprathrin, imidacloprid, phosmet, thiamethoxam and zeta-cypermethrin. Spirotetramat is also registered for use in Florida and Texas but is no longer registered for use in California. All insecticides currently used to control Asian citrus psyllid on bearing trees are broad-spectrum foliar insecticides applied to control adult psyllids prior to the presence of new flush of foliage growth. There are currently no effective insecticides to control juvenile psyllids. Control of overwintering adult psyllid populations is necessary to reduce populations on spring flushes. Early season control is necessary to suppress populations and reduce the need for psyllid control during bloom when most insecticides cannot be used for psyllid control due to bee toxicity.
4. Scale – California red scale, an armored scale, is distributed throughout the citrus-growing regions of California except in the Coachella Valley where they are under an eradication program. Citricola scale, a soft scale, can be a serious pest of citrus in the San Joaquin Valley. California red scale attacks all aerial parts of the tree by sucking on plant tissues. Heavily infested fruit may be downgraded in the packinghouse and, if populations are high, serious damage can occur to trees (leaf yellowing and drop, dieback of twigs and limbs, and occasional death of the tree). Tree damage is most likely to occur in late summer and early fall when scale populations are highest and moisture stress on the tree is greatest. Citricola scale may reduce tree vigor, kill twigs, and reduce flowering and fruit set when occurring in high infestations. Citricola scale feeding results in excretion of honeydew and accumulation on leaves and fruit. Sooty mold grows on honeydew and interferes with photosynthesis in leaves and causes fruit to be downgraded in quality during packing. Oil is the most selective pesticide for scale control but only suppresses populations and requires frequent reapplication. IGRs, such as pyriproxyfen and buprofezin, are safe to most beneficial insects but are toxic to the beneficial vedalia beetle (a species of lady beetle) which is needed to control cottony cushion scale. Furthermore, observations indicate that red scale may be developing resistance to pyriproxyfen. Spirotetramat is safe to beneficial insects and vedalia beetles but cannot be used in California. Organophosphate and carbamate insecticides are broad spectrum and toxic to most natural enemies. In addition, a number of populations of red scale and citricola scale are now resistant to either organophosphate and/or carbamate insecticides.

Neonicotinoids can suppress scale but are toxic to natural enemies and disrupt biological control of cottony cushion scale.

5. Sulfoxaflor is highly effective against the target pests, including resistant populations, and offers acceptable and only short-term impact on natural enemy populations. Sulfoxaflor would replace a significant portion of acreage currently treated with chlorpyrifos.

BEAD's Response: The percentage of total citrus acreage treated nationally for mealybug is 11%, for scale -77.8%, and for aphids - 14.7%) (based on data for orange, grapefruit, and lemon production in Florda, California, Texas and Arizona). The percentage of total acreage treated for psyllid is 100% (based on data for Florida and Texas) (USEPA, 2012).

1. Aphids are primarily pests of citrus in California and Florida. Aphids are generally not a problem on citrus except on young trees because their populations decline when the foliage hardens off. Natural enemies normally control aphid populations, and a spray is rarely warranted. The percentage of total acres treated for aphids in California and Florida is 13.3% and 15.4%, respectively. Populations of cotton aphids in the San Joaquin Valley have been shown to have resistance to organophosphate, carbamate, and pyrethroid insecticides (UC IPM 2008d). In addition, a study by Cutler et. al. (2009) determined that sublethal exposure to imidacloprid and azadirachtin can induce hormetic responses in aphids (e.g. increase in reproduction). BEAD concludes that sulfoxaflor would be most likely to replace either imidacloprid or thiamethoxam for aphid control in citrus. In addition, due to the lack of cross-resistance with neonicotinoids, sulfoxaflor would not only add an additional control option but would provide an alternative to prevent resistance development to the currently used neonicotinoids.
2. Mealybug can exhibit heavy densities in greenhouses but generally are not a problem in citrus production. Mealybugs are primarily managed by conserving their natural enemies and reducing ant populations and dust problems. Treatment is rarely required. The percentage of total acreage treated for mealybug in citrus production in Arizona, California, Florida and Texas is 0.1%, 5.2%, 3.3%, and 2.3%, respectively. In two studies submitted by the registrant, sulfoxaflor performed equal to chlorpyrifos and pyriproxyfen. As chlorpyrifos is the current market leader insecticide to control mealybug in citrus, sulfoxaflor does have the potential to effectively displace/reduce the amount of chlorpyrifos currently used to control mealybug in those rare cases when it is used. It also has the potential to at the least provide an alternative to manage mealybug and minimize potential insect resistance to chlorpyrifos.
3. Psyllids are currently important pests in Florida and Texas citrus with 100% of acres treated to prevent citrus greening disease. In contrast, due to the absence of citrus greening disease, only 2% of California citrus acreage is treated to control psyllids. Currently, treatment in California is limited to prevention of spread of Asian citrus psyllid from the quarantine zone. However, the low percent of acres treated in California is dependent upon the effectiveness of the California quarantine program. Overall, with the exception of chlorpyrifos, psyllid resistance to most insecticides is considered low at this time (Boina et.al. 2009). In Florida, broad-spectrum foliar sprays are most effective when used to control adult psyllids prior to the presence of new flush. Once psyllids begin reproducing on new flush, it becomes increasingly difficult to gain control of rapidly increasing populations. Psyllid management programs should begin by first

targeting overwintering adult psyllids during the winter months when the trees are not producing flush (Rogers et.al., 2012). By eliminating these overwintering adults, psyllid populations will be greatly reduced on the following spring flushes. Targeting psyllids early in the year should provide enough suppression in psyllid populations to reduce the need for psyllid sprays during bloom (Rogers et.al., 2012). In 2 field trials submitted in support of the registration, sulfoxaflor performed equal to chlorpyrifos. In addition, sulfoxaflor provided equal length of psyllid control to the market leader insecticides for adults (25-31 days) but far exceeded all but zeta-cypermethrin for control of nymphs (up to 40 days) when compared to the untreated check (Stansley et.al., 2012). While BEAD concludes that sulfoxaflor is effective for psyllid control, based on the number of effective alternatives, BEAD believes that sulfoxaflor will most likely only provide an additional insecticidal tool.

4. Scale insects are predominantly pests in California with 85.7% of total citrus acreage receiving insecticide application. In contrast, only 1.3% of the total citrus acreage is treated in Florida and 7.6% in Texas. In Florida, scale insects are primarily under biological control and oversprays of pesticides are not recommended (Fasulo and Brooks, 2010). In the San Joaquin Valley of California, a number of populations of armored scale have been found to be resistant to the organophosphates chlorpyrifos (Lorsban) and methidathion (Supracide) and to the carbamate carbaryl (Sevin). Scales have not developed resistance to oil sprays or insect growth regulators (buprofezin - Applaud), but observations indicate that resistance to pyriproxyfen (Esteem) may be developing (UC IPM 2009c). A number of populations of citricola scale have been found to be resistant to the organophosphate chlorpyrifos (Lorsban). Thus, low rates of this insecticide would be ineffective and high rates only suppress citricola scale for a single year (UC IPM 2009d). Sulfoxaflor performed equal to chlorpyrifos and pyriproxyfen in 3 field tests included in the submission package. BEAD concludes that sulfoxaflor can provide effective control of scales in citrus and could potentially reduce current dependence on chlorpyrifos.
5. BEAD agrees with the registrant that sulfoxaflor will be useful to control aphids, scale, psyllid, and mealybugs in citrus production.

Table 4. Market leader insecticides for pest control on citrus.

Pest[1]	Insecticide[2]	Crop Acres Treated (%)[3,4,5]	Strength[6,7,8,9,10,11,12,13]	Weakness[6,7,8,9,10,11,12,13]
Aphids	Abamectin	11.2		
	Acetamiprid	9.3		
	Chlorpyrifos	8.6	Broad spectrum	Cotton aphids in the San Joaquin Valley have shown resistance to organophosphate, carbamate, and pyrethroid insecticides. May increase populations of spider mites.
	Imidacloprid	19.1		Limit on use during bloom, disruptive to natural enemies. Should be applied prior to or at onset of pest population.
	Petroleum oil	17.0	Selective, low impact on beneficials	Requires reapplication, serious phytotoxicity to green lemons, toxic to predatory mites.
	Thiamethoxam	20.1		Cannot be applied during bloom
Mealybugs	Chlorpyrifos	45.8	Broad spectrum	May increase spider mite populations.
	Imidacloprid	17.1		Limit on use during bloom, disruptive to natural enemies
	Petroleum oil	22.0	Selective, short impact on beneficials	Requires reapplication, phytotoxic to green lemons, toxic to predatory mites
	Spirotetramat	11.3	Selective, No impact on vedalia beetles for control of cottony cushion scale	Not registered for use in CA
Psyllid (Asian citrus)	Abamectin	12.9		
	Dimethoate	6.0	Very effective against adult psyllids	Only provide 4-6 weeks control. Very toxic to natural enemies.
	Fenpropathrin	7.1	Very effective against adult psyllids.	Only provide 4-6 weeks control. Very toxic to natural enemies.
	Imidacloprid	11.9	85% effective against nymphs.	Limit on use during bloom due to bee toxicity. Foliar treatment is more disruptive to natural enemies than systemic treatment.
	Petroleum oil	16.6	Effective against adult psyllids	No more than 2 weeks protection, phytotoxic to green lemons.
	Zeta-cypermethrin	16.6	Very effective against adult psyllids.	Only provide 4-6 weeks control. Very toxic to natural enemies.
Scale (Citricola and California red)	Chlorpyrifos	26.3	Selective, many natural enemies have developed resistance and short persistence	Some populations have developed resistance. May increase spider mite populations.
	Petroleum oil	39.0	Relatively non-toxic to natural enemies because of brief residual activity	Temperature must be less than 95 degrees. Only reduces numbers and may require reapplication 2 times per year. Recommended to be applied with carbaryl. Toxic to predatory mites.
	Pyriproxyfen	14.3	Safe for parasitic wasps	Toxic to vedalia beetles needed for control of cottony cushion scale. Observations indicate that resistance may be developing. Not effective for adults

1 Does not include pests where control is limited to suppression.
2 Only includes alternatives which account for greater than 5 percent of treated acres
3 Does not reflect total crop treated. Based only on the crop acres treated for the specific pest
4 Adjusted to reflect cancellation of endosulfan
5 USEPA. 2012. Proprietary Data for 2009-2011.

[6] UC IPM. 2008d. UC Pest Management Guidelines – Citrus – Aphids.
[7] UC IPM. 2009c. UC Pest Management Guidelines – Citrus – California Red Scale and Yellow Scale.
[8] UC IPM. 2009d. UC Pest Management Guidelines – Citrus – Citricola Scale.
[9] UC IPM. UC IPM. 2008e. UC Pest Management Guidelines – Citrus – Mealybugs.
[10] UC IPM. 2009b. UC Pest Management Guidelines – Peppers – Whiteflies.
[11] USDA. 2009. Pest Management Strategic Plan for Citrus Production in California.
[12] USDA. 2003e. A Texas Citrus Pest Management Strategy.
[13] Browning et al. 2012. 2012 Florida Citrus Pest Management Guide: Soft-Bodied Insects Attacking Foliage and Fruit

Benefits Assessment for Cotton

Limitations: This analysis is primarily focused on tarnished plant bugs in the mid-south production region. BEAD found that an urgent, non-routine situation existed for the use of sulfoxaflor against tarnished plant bug in Mississippi, Louisiana, Arkansas, and Tennessee in 2012.

Pest(s): – cotton aphid, tarnished plant bug, western tarnished plant bug, brown stink bug (suppression only), silverleaf whitefly, southern green stink bug, sweet potato whitefly, thrips (suppression only)

Registered Alternatives: Registered alternatives for the labeled pests are presented in Table 5.

Registrant's Justification: The efficacy of registered alternatives controlling the target pests on cotton was reviewed by the registrant and the benefits claimed by the registrant are:

1. More insecticides are applied for control of plant bugs than control of any other insect pest in cotton. The number of insecticide applications and costs of control have increased.
2. Tarnished plant bugs were estimated to infest 1.3 million acres in Louisiana, Mississippi, Arkansas, and Tennessee, nearly all cotton production acreage in this region. Yield losses due to plant bug were estimated at 79,000 bales (nearly $25 million) and insecticide and application costs were estimated at nearly $44 million in 2009
3. Tarnished plant bug populations express varying levels of resistance to organophosphate, pyrethroid, and carbamate insecticides.
4. Due to boll weevil eradication and the adoption of transgenic Bt cotton, fewer insecticides are being applied which in turn favor development of tarnished plant bugs and western tarnished plant bugs.
5. While control of western tarnished plant bug has been achieved in Arizona using flonicamid, growers cannot rely on a single insecticide for long-term pest management. Similarly, while California has relied on pyrethroids to control western tarnished plant bug, pyrethroids are disruptive to beneficial populations and IPM programs and may flare mites and aphids. In addition, surveys in California indicate that western tarnished plant bugs are developing resistance to pyrethroids with shorter residual control and need for retreatment.
6. With multiple mechanisms of resistance in populations of plant bugs, many of the recommended insecticides no longer provide consistent control, and novel compounds are desperately needed. Sulfoxaflor is highly effective against plant bugs and offers a novel mode of action to manage resistant populations.

BEAD's Response: BEAD conducted a review of an emergency exemption request assessment for the use of sulfoxaflor on mid-south cotton (Louisiana, Mississippi, Tennessee, and Arkansas) to control tarnished plant bug in 2012 (Atwood and Faulkner 2012).

1. *Pest Information* (USDA 2003d): Plant bugs lay their eggs inside tender and succulent cotton stems, making them very difficult to detect in the field. Generally plant bugs will hatch in 10 to 14 days; they will spend 10 to 18 days as nymphs; with five nymphal stages. Tarnished plant bugs overwinter as adults in ground trash near host plants.

   Severe plant bug infestations can develop quickly because bug populations may build on other host plants and then move into cotton. Wild and cultivated plant hosts include most common roadside weeds and cultivated crops such as alfalfa, soybean, vegetables and corn. Plant bugs can move onto cotton from proximate wild host plants or crops when those plants senesce or are mowed or sprayed with herbicides. Growers may be faced with a severe plant bug infestation just days after having relatively clean fields. Infestations occur throughout crop development, but the period from the seedling stage until the second week of flower is when plant bugs are of greatest concern in most mid-south production systems. In recent years, the reduced spray environment fostered by the Boll Weevil Eradication Program and transgenic Bt cotton have been such that plant bug population densities build in July and August to levels that potentially could result in economic damage.

   Plant bugs feed using the process of extra-oral digestion or solid-to-liquid feeding. Their piercing mouthparts penetrate and macerate plant tissues and at the same time delivering chemically macerating digestive enzymes. The resulting concentrated plant slurry is then sucked up by the bug. Feeding sites include fruit and floral tissues and meristematic cells.

   In pre-squaring cotton, the terminal portions of plants are preferred feeding sites. Injury from plant bug feeding at this crop stage can cause loss of apical dominance, which can result in multiple terminals per plant, a condition sometimes referred to as "crazy cotton". Reduced growth following terminal injury of pre-squaring cotton can delay development of squares, crop maturity and reduce yield if optimal growing conditions do not allow for compensatory growth. As the cotton crop develops, squares become important feeding sites.

   Small squares will shed following plant bug feeding, but larger squares typically are more tolerant. The probability of square abscission following tarnished plant bug feeding is a function of anther size. When anthers are hardly visible, the bug feeds on the totality of the floral bud. As the square grows, the anthers reach a large enough size for the bug to feed on the individual pollen sack. When tarnished plant bug feeding is localized on the anthers, shed rarely happens; however, squares with extensive anther damage may shed as bolls. Flowers may be attacked by plant bugs, with feeding resulting in warty growths on flower petals and brown spots on stamens and pistils. Atwood and Faulkner (2012) determined a potential yield loss of 15% per acre in Mississippi cotton directly related to the tarnished plant bug.

2. *Biological/Cultural Control:* Biological alternatives cannot adequately control tarnished plant bug. However, reduced crop damage and insecticide applications against the tarnished plant bug can be achieved through early planting.

3. *Required Number of Insecticide Applications:* Cotton consultant survey data (2007) submitted by Mississippi indicates that 77% of Delta cotton acreage receives greater than 7 insecticide applications per year to control tarnished plant bug with a range of 7 to 16 applications. BEAD proprietary application data for the counties included in the new submission indicates an average insecticide application range of 3.8 to 6.4 for the same counties between 2007 and 2010. However, BEAD believes that state sampling data may be more extensive than that provided by the proprietary database and therefore more indicative of actual insecticide use in Mississippi. Therefore, BEAD believes the average of 8 applications indicated by Mississippi is a more accurate assessment of insecticide use against the tarnished plant bug in the delta region of Mississippi.

4. *Insecticide Resistance:* BEAD review of the two previous submissions in 2011 requesting the use of sulfoxaflor to control tarnished plant bug concluded that sufficient alternatives were available to provide season-long control of tarnished plant bug (7-10 insecticide applications). These insecticides included novaluron, bifenthrin/imidacloprid, beta-cyfluthrin, thiamethoxam/lambda-cyhalothrin, clothianidan (supplemental labeled through 2012), dicrotophos, and acephate. However, the revised applications from Mississippi in 2012 provided additional insight into the extent and magnitude of resistance of the tarnished plant bug to currently registered insecticides.

   Mississippi indicated that synthetic pyrethroids are no longer recommended for tarnished plant bug control. A summary of trials conducted from 2004 to 2010 at the Stoneville, MS Extension Center confirms this conclusion by showing that pyrethroids only provided control in the range of 0 to 47% between 2004 and 2010. In addition, data submitted for 2007 field trials using acephate and bifenthrin (the most active pyrethroid), shows inability to maintain populations below the action threshold level when applied either alone or in combination with acephate. In addition, as co-application of mixtures of neonicotinoid and synthetic pyrethroids has become a primary means to control tarnished plant bugs, application of pyrethroids as an individual application is limited due to seasonal restrictions on total amount applied.

   Additional data in the submission, from laboratory and field studies, verify claims that effectiveness of acephate and dicrotophos has been greatly reduced since 2005. In lab studies, acephate was not able to provide in excess of 48% tarnished plant bug mortality when applied at maximum field rates. Field studies conducted in Stoneville, MS also show decreased activity of acephate and dicrotophos (approximately 39% and 51% reduction in percent control between 2005 and 2010, respectively). Yield losses in the same studies between the same periods were approximately 30% regardless of insecticide used. This data confirms that organophosphates are no longer providing effective control of the tarnished plant bug in Mississippi.

The third primary insecticide class which has been used to control tarnished plant bug is the neonicotinoids. Mississippi indicates that tarnished plant bug control has always been inconsistent with this class of insecticides. However, neonicotinoids are also used to control thrips and cotton aphid prior to the first sprays needed for tarnished plant bugs, so some in-field selection of populations is occurring, as well as limiting the available total active ingredient of these products that can be used later in the season. Some populations of tarnished plant bugs are expressing variation in responses to these products (thiamethoxam, imidacloprid, and acetamiprid) as well. In addition, one population in Mississippi has shown resistance to thiamethoxam, the most active neonicotinoid against tarnished plant bug. While field control failures have not been documented using thiamethoxam, continued reliance on neonicotinoids as the primary tool for controlling tarnished plant bug may expedite resistance to this class of insecticides.

Novaluron is able to control small tarnished plant bug nymphs but is not effective against large nymphs or adults. Due to the rapid development of tarnished plant bugs, this makes application timing critical to target eggs and small nymphs in order to obtain effective control. Due to eggs being laid in plant tissue and not readily visible, proper timing to achieve maximum control of small nymphs is complicated and can be unreliable. In order to be effective, novaluron is best applied in conjunction with an adulticide which further limits the pool of available seasonal insecticide applications.

5. *Conclusion*: BEAD concluded that the situation described in the emergency exemption request was non-routine, urgent, and likely to result in significant economic loss. Season long control of the tarnished plant bug in Mississippi at levels below the economic threshold and which do not result in an economic loss was not deemed achievable with the currently registered insecticides and warranted the request for sulfoxaflor. Furthermore, BEAD concluded that the tarnished plant bug situation was not unique to Mississippi and was applicable to all contiguous cotton producing counties in the Delta region of the United States to also include the states of Arkansas, Tennessee, and Louisiana.

6. Based on the findings of this review, BEAD believes that sulfoxaflor will be an important insecticide for control of insect pests on cotton.

Table 5. Market leader insecticides for pest control on cotton.

Pest[1]	Insecticide[2]	Market Share (%)[3,4,5]	Insecticide Weakness
Cotton aphid	Acephate	18.2	Resistant populations
	Acetamiprid	5.6	Populations expressing resistance
	Aldicarb	7.6	May no longer be available
	Dicrotophos	9.4	Resistant populations
	Imidacloprid	14.0	Populations expressing variation in response
	Thiamethoxam	28.7	Limit to annual total application due to primary use for at plant control of thrips. Insect resistance reported
Southern green stink bug	Bifenthrin	12.3	No recommended due to ineffective control and causes aphid outbreaks
	Zeta-cypermethrin	87.7	No recommended due to ineffective control and causes aphid outbreaks
Tarnished plant bug	Acephate	21.8	Resistant populations
	Bifenthrin	11.2	No recommended due to ineffective control and causes aphid outbreaks
	Dicrotophos	15.4	Resistant populations
	Imidacloprid	12.8	Populations expressing variation in response
	Thiamethoxam	18.2	Limit to annual total application due to primary use for at plant control of thrips. Insect resistance reported.
Whitefly (Silverleaf and Sweet potato)	Acephate	6.3	Resistant populations
	Acetamiprid	22.9	
	Buprofezin	13.6	
	Cyfluthrin	8.2	No recommended due to ineffective control and causes aphid outbreaks
	Dicrotophos	6.0	Resistant populations
	Flonicamid	8.0	
	Pyriproxyfen	10.9	

1 Does not include pests where control is limited to suppression (thrips).
2 Only includes alternatives which account for greater than 5 percent of treated acres
3 Does not reflect total crop treated. Based only on the crop acres treated for the specific pest
4 Adjusted to reflect cancellation of endosulfan
5 USEPA. 2012. Proprietary Data for 2009-2011.

Importance of Bee Pollination

Table 6 provides estimates of the importance of honey bees as pollinators of the crops assessed in this benefit analysis.

Table 6. Importance of honey bees to crop pollination for assessed crops.

Crop Group	Crop	Dependence of Crop On Insect Pollination[1] (%)	Proportion of Pollinators That Are Honey Bees[1] (%)	Percentage Pollinated by Honey Bees[1]	Acres Grown[2]
Cucurbit Vegetable	Cucumber	90	90	81	151,759
	Cantaloupe	80	90	72	84,290
	Honeydew Melon	80	90	72	17,344
	Pumpkin	90	10	9	92,955
	Squash	90	10	9	54,454
	Watermelon	70	90	63	142,359
Citrus	Grapefruit	80	90	72	102,578
	Lemon	20	100	20	66,972
	Lime	30	90	27	1,251
	Orange	30	90	27	785,856
	Tangelo	40	90	36	9,694
	Tangerine	50	90	45	36,965
	Temple	30	90	27	1,211
Cotton	Cotton	20	80	16	10,493,238

1. Morse and Calerone. 2000 The Value of Honey Bees As Pollinators of U.S. Crops in 2000.
2. USDA/NASS. 2009. 2007 Census of Agriculture.

Fruiting Vegetables

The flower structure of fruiting vegetables is such that only the pollen from their own stamens can reach their stigma. These flowers are called self-pollinated. In addition, flowers of fruiting vegetables are not especially attractive to honey bees. Unlike tomatoes, peppers and eggplant may benefit from honey bee pollination with a resulting increase in yield. However, honey bee pollination of these plants is not essential for crop production. Use of sulfoxaflor on fruiting vegetables is not likely to result in exposure to honey bees.

Cucurbit Vegetables

Melon and cucumber flowers are pollinated exclusively by honey bees and other insect pollinators. They are not wind or self-pollinated. Insects are required for pollen transfer because of the large size of the pollen grains, their stickiness, and the way they are released from the anthers. Also, since these plants typically produce only small amounts of pollen, pollinators are needed to efficiently transfer pollen from one flower to the next. While wild bees or distant honey bee colonies may suffice for small melon or cucumber fields, they may be inadequate for the commercial grower whose income depends on substantial yields of high quality fruit (Hodges and Baxendale, 2012).

The individual flowers of cucurbits remain open only for a single day. If they are not pollinated during that time, the flowers abort and drop from the vine. When incomplete pollination occurs, fruit do not develop properly. Because many seeds form within each fruit and each pollen grain

is responsible for the development of a single seed, inadequate pollination results in small or misshapen fruit and low yields of marketable fruit.

Cucurbit flowers open shortly after sunrise and remain open until late afternoon or early evening, so each flower is open for only a few hours. The honey bee is the most common and effective cucurbit pollinator. Honey bee activity closely coincides with the period when the flower is open. Honey bees begin to visit flowers an hour or two after sunrise and continue to visit until mid-afternoon. If temperatures are very warm, bee activity may decline about noon (Hodges and Baxendale, 2012).

Researchers have found that it takes at least nine honey bee visits per flower to pollinate cucumbers adequately. Since each bee will visit about 100 flowers per foraging trip, usually at least one strong hive per acre is required. Bees are most efficient if they can forage within 200 yards of the hive. Honey bee colonies should be moved into position near the field about the time the first female flowers are seen. If the bees are moved in too early, they may find other attractive flowering plants in the area and not work the cucurbits. Hives can be removed from melon fields when flowering begins to diminish or when the vines begin to break down. Leave colonies in cucumber fields until a day or so before the last picking. (Hodges and Baxendale, 2012)

Based on this information, BEAD concludes that honey bee pollination is important for the production of cucurbit vegetables, particularly cucumbers and melons. However, based on the phenology of the crop and associated honey bee activity, honey bee exposure to sulfoxaflor can be greatly reduced by restricting applications to late afternoon when honey bees are not likely to be active.

Citrus

The pollination requirements for citrus are complex because of the number of citrus varieties that have been developed. Each variety has its own characteristics and pollination requirements. Recommendations for one variety may not be applicable to another variety.

From a grower's present perspective, information on citrus pollination may seem academic. Most citrus is, fortuitously for growers, superior in nectar production, responsible in good years for a premium, high quality honey crop. Thus, there are always plenty of bees in the groves; whatever pollination is needed is right at hand. And best of all, it's provided free for the producer in exchange for nectar that would otherwise go to waste (Sanford, 2003). The key point is that commercial beekeepers seek out citrus groves for honey production rather than citrus growers seeking commercial bee hives for pollination.

Flowering influences the timing of important and costly operations such as the spring pesticide applications, the placing of beehives for citrus honey production, and probably the employment of labor for harvesting. Although the duration of bloom in individual groves is usually 12 to 20 days, citrus groves on a statewide basis in Florida have a moderate amount of bloom for an average of 41 days, approximately from March 5 to April 15. Bloom may be more than twice as

abundant in a year of maximum bloom as compared to a year of minimum bloom (Simanton, 1969).

In summary it may be concluded that honey bees are important in the pollination of citrus, though some varieties benefit more than others. As bees are always present in citrus groves due to their rich nectar resources, pollination in citrus becomes little more than an academic exercise. Major questions, however, remain related to bee distribution in citrus groves and management methods which would optimize their pollinating activities. Nevertheless, based on the periodicity of bloom noted for citrus in Florida, honey bee exposure to sulfoxaflor can be greatly reduced by restricting applications to the non-bloom period.

Cotton (Danka 2005)

Yield of upland cotton may increase by 3-30% following pollination by honey bees. However, honey bees only rarely collect cotton pollen in most regions of the United States and this behavior probably restricts their pollination effectiveness.

Bee Pollination – Conclusion

Overall, honey bees are only essential to the production of cucurbit vegetables. However, this is not to say that honey bee pollination of fruiting vegetables, citrus, and cotton has no benefit. BEAD concludes that due to crop phenology and bee importance to individual crops, sulfoxaflor application should result in little honey bee exposure when restricted to times when flowers are not present or late afternoon sprays with reduced bee activity.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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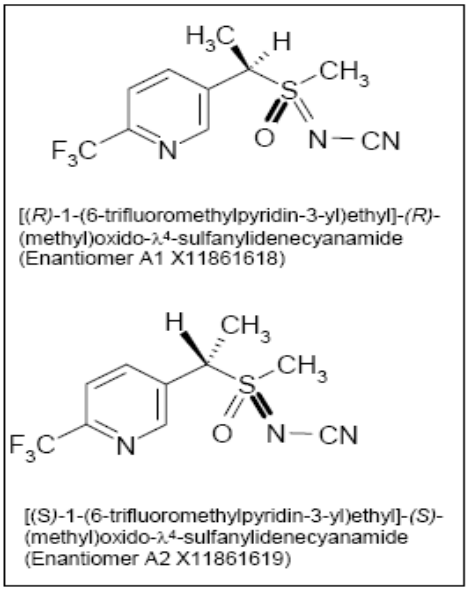
OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration



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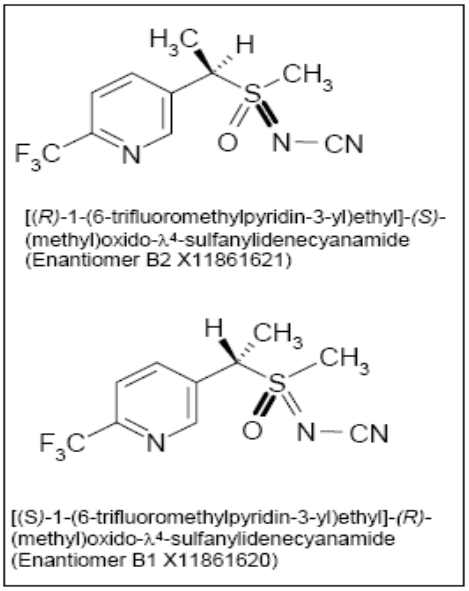

Diastereomer 2
X11546258

Sulfoxaflor: A 50:50 Mixture of Diastereomer 1 and 2

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1. EXECUTIVE SUMMARY

1.1. Nature of Chemical Stressor

Sulfoxaflor (N-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-lambda 4-sulfanylidene]) is a new class of insecticide and is currently the only member of the sulfoxamine subclass of neonicotinoid insecticides.[1] It is considered an agonist of the nicotinic acetylcholine receptor (nAChR) and exhibits excitatory responses including tremors, followed by paralysis and mortality in target insects. In laboratory experiments, sulfoxaflor has been highly efficacious against target insects that display resistance to neonicotinoids such as imidacloprid, which is classified by the Insect Resistance Action Committee (IRAC) as subclass 4A. Sulfoxaflor consists of two diastereomers in a ratio of approximately 50:50 with each diastereomer consisting of two enantiomers.

Sulfoxaflor is formulated as suspensions concentrate and water dispersible granules and is proposed for application as a liquid spray on a variety of crops. The proposed crops include beans, berries, canola, citrus, cotton, fruits (pome/stone), ornamentals, grains "small", soybeans, tree nuts, turf, vegetables (brassica "leafy" bulb, cucurbits, fruity including okra, leafy, and root & tuber) and watercress. Sulfoxaflor is systemically distributed in plants. The chemical acts through both contact action and ingestion and provides both rapid knockdown (symptoms are typically observed within 1-2 hours of application) and residual control (generally provides from 7 to 21 days of residual control).

Transformation products of sulfoxaflor in the environment include: X11719474 (X-474; "major to dominant"), X11579540 (X-540; "minor to major"), and X11579457 (X-457; "minor"). Following consideration of exposure and toxicity for the residues of interest (that is parent, X-474 and X-540), the stressor of concern is defined as follows:

(1) For aquatic organisms: parent sulfoxaflor plus its degradate, X-540; and

(2) For terrestrial organisms: parent sulfoxaflor only.

With the exception of X-474, this assignment of stressors of concern for ecological risk is consistent with the risk assessment approach used by the Health Effects Division for sulfoxaflor (D396249). For terrestrial and aquatic ecological receptors, available evidence indicates that the X-474 degradate does not share the same MOA as the parent and is much less toxic based on measures of effect relevant to ecological risk assessment. Detailed data and information concerning this decision are presented in the problem formulation section of this document.

[1] http://www.irac-online.org/eClassification/

1.2 Potential Risks to Non-target Organisms

Table 1 provides a summary of the environmental risk conclusions for aquatic and terrestrial organisms, based on risk quotient (RQ) values and whether they exceed levels of concern (LOCs) for Federally-listed threatened and endangered species (hereafter referred to as "listed" species) and non-listed species.

Table 1. Summary of Ecological Risk Conclusions for the Proposed Sulfoxaflor Uses*

Taxonomic Group	Summarized Risk Characterization and Major Uncertainties
Fish and Aquatic Invertebrates (freshwater and saltwater)	The potential for acute or chronic risk is considered low, as acute or chronic RQ values do not exceed the risk to listed species LOC of 0.05.
Aquatic and Terrestrial Plants	The potential for risk is considered low, as RQ values do not exceed the LOC values for listed and non-listed aquatic or terrestrial plants.
Birds**	A potential for acute risk to birds is identified. Specifically, acute, dose-based RQ values calculated using a refined dissipation half-life (DT_{50}) exceed the risk to listed species LOC of 0.1 for at least one avian dietary category and size class across all uses. This risk finding is uncertain because the acute toxicity endpoint used to derive the avian RQ values represents a "non-definitive" endpoint and is based on a threshold for treatment-related increases in regurgitation. Acute and chronic diet-based RQ do not exceed applicable LOCs.
Mammals	A potential for chronic risk to mammals is identified. Specifically, chronic dose-based RQ values up to **3.8** were determined using a refined DT_{50} and exceed the risk to listed species LOC of 0.1 for at least one mammalian dietary category and size class across all uses. For some crops, information from residue-decline trials indicates relatively short half lives (*e.g.,* a few days), particularly on foliage. For these crops, there is uncertainty regarding whether the relatively short duration of exposure expected in the field would elicit similar reproductive effects as the chronic, 2-generation study with the rat where animals are fed treated diets continuously.
Bees	A potential for risk to honey bees is identified based on Tier 1 assessment results. Tier 1 acute oral RQ values range from <**0.8 to 5.7** across all larval and adult castes examined. Results from Tier 2 semi-field studies indicate direct effects of sulfoxaflor on adult foragers is likely to be short-lived at application rates of 3-67% of the single maximum rate proposed for the US. These studies were unable to preclude risk to developing brood or long-term colony health from the proposed sulfoxaflor applications due to limitations associated with their design and conduct.

* includes: Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass; (Beans, Berries, Soybeans, Veg.-Brassica, Veg.-Bulb, Veg.-Leafy, Veg.-Root/Tuber, Veg.-Fruiting, Veg.-Cucurbit, Watercress, Cotton, Canola and Grains

** In absence of data, birds are used as a surrogate for terrestrial phase amphibians and reptiles.

1.3 Conclusions - Exposure Characterization

Sulfoxaflor has a low potential for volatilization from dry and wet surfaces (vapor pressure= 1.9 x 10^{-8} torr and Henry's Law constant= 1.2 x 10^{-11} atm m^3 $mole^{-1}$, respectively at 25 °C). The chemical is characterized by a water solubility ranging from 550 to 1,380 ppm. Partitioning coefficient of sulfoxaflor from octanol to water (K_{ow}= 6) suggests low potential for bioaccumulation in aquatic organisms such as fish.

Sulfoxaflor reaching the soil system is subjected to rapid aerobic bio-degradation ($t_{½}$ <1 day) while that reaching foliage may enter the plant tissue and persist much longer. Sulfoxaflor has shown to be stable to hydrolysis/ photolysis on soil and in aquatic environments. In field studies, sulfoxaflor has shown similar vulnerability to aerobic bio-degradation in nine out of ten terrestrial field dissipation studies on bare-ground/cropped plots (half-lives were <2 days in nine cropped/bare soils in CA, FL, ND, ON and TX and was 8 days in one bare ground soil in TX).

The chemical can be characterized by very high to high mobility (K_{foc} ranged from 11-72 mL g^{-1}). Rapid soil degradation is expected to limit chemical amounts that may potentially leach and contaminate ground water. Contamination of groundwater by sulfoxaflor will only be expected when excessive rain occurs within a short period (few days) of multiple applications in vulnerable sandy soils. Contamination of surface water by sulfoxaflor is expected to be mainly related to drift and very little due to run-off. This is because drifted sulfoxaflor that reaches aquatic systems is expected to persist while that reaching the soil system is expected to degrade quickly with slight chance for it to run-off.

In contrast to sulfoxaflor parent, the major degradate X-474 and two other degradates (X-540 and X-457) are expected to be highly persistent in aerobic soil/aquatic systems. Adsorption data for these degradates indicate that they can be characterized by very high to high mobility for X-474 (K_{foc} ranged from 7-68 mL g^{-1}) and very high mobility for X-457 and X-540 (K_{foc} ranged from 2-44 mL g^{-1} for X-457 and K_{foc} ranged from 1-25 mL g^{-1} for X-540). Both surface and ground water contamination is expected from these three degradates following leaching drift/run-off events. The major degradate X-474 is expected to dominate the exposure resulting from use of sulfoxaflor.

1.4 Conclusions - Effects Characterization

Based on available data, sulfoxaflor is slightly toxic to practically non-toxic to fish and freshwater water column dwelling aquatic invertebrates on an acute exposure basis. It is also practically non-toxic to aquatic plants (vascular and non-vascular). Sulfoxaflor is highly toxic to saltwater invertebrates (mysid shrimp; *Americamysis bahia*) on an acute exposure basis. The NOAEC for chronic toxicity of sulfoxaflor to freshwater benthic insects (midge, *Chironomus riparius*) is 0.037 mg a.i./L in porewater. The high toxicity of sulfoxaflor to mysid shrimp and benthic aquatic insects relative to the water flea (*Daphnia magna*) is consistent with the toxicity profile of other insecticides with similar MOAs on the insect nAChR such as neonicotinoid insecticides.

For birds and mammals, sulfoxaflor is classified as moderately toxic to practically non-toxic on an acute exposure basis. The threshold for chronic toxicity (NOAEL) to birds is 200 ppm and that for mammals is 100 ppm in the diet. Sulfoxaflor did not exhibit deleterious effects to terrestrial plants at or above its proposed maximum application rates.

For bees, sulfoxaflor is classified as very highly toxic with acute oral and contact LD_{50} values of 0.05 and 0.13 µg a.i./bee, respectively, for adult honey bees (*Apis mellifera*). For larvae, a 7-d oral LD_{50} of >0.2 µg a.i./bee was determined (45% mortality occurred at the highest treatment of 0.2 µg a.i./bee). Its primary metabolite (X-474) is practically non-toxic to the honey bee. This lack of toxicity is consistent with the cyano-substituted neonicotinoids where similar cleavage of the cyanide group appears to eliminate their insecticidal activity. The acute oral toxicity of sulfoxaflor to adult bumble bees (*Bombus terrestris*) is similar to the honey bee; whereas its acute contact toxicity is about 20X less toxic for the bumble bee. Sulfoxaflor did not demonstrate substantial residual toxicity to honey bees exposed via treated and aged alfalfa (*i.e.*, mortality was ≤15% at maximum application rates).

A detailed analysis of six available Tier 2 semi-field (tunnel) studies was conducted in order to confirm or refute the risks identified from the Tier 1 assessment on honey bees. Five of the six semi-field studies used application rates ranging from 3 to 67% of the single maximum rate of 0.133 lb a.i./A proposed for the US. The one semi-field study that used maximum US application rates was intended for quantifying residues in plant matrices, and thus, has limited biological effects information.

In considering the available information from the semi-field tunnel studies, the following conclusions were reached:

- **Adult mortality, flight activity, behavioral abnormalities.** At the application rates used (3-67% of US maximum), the direct effects of sulfoxaflor on adult forager bee mortality, flight activity and the occurrence of behavioral abnormalities is relatively short-lived, lasting 3 days or less. Direct effects are considered those that result directly from interception of spray droplets or dermal contact with foliar residues. The direct effect of sulfoxaflor on these measures at the maximum application rate in the US is presently not known.

- **Development of Brood.** The effect of sulfoxaflor on brood development is considered inconclusive due to numerous limitations in the design and conduct of the available studies. These limitations include poor performance of control hives, lack of (or short) post-application observation period in order to detect brood effects, and lack of a concurrent control.

- **Colony Strength.** When compared to controls hives, the effect of sulfoxaflor on honey bee colony strength when applied at 3-32% of the US maximum proposed rate was not apparent in most cases. When compared to hives prior to pesticide application, sulfoxaflor applied to cotton foliage up to the maximum rate proposed in the US resulted

in no discernible decline in mean colony strength by 17days after the first application. Longer-term results were not available from this study nor were concurrent controls included.

1.5 Data Gaps and Uncertainties

1.5.1 Environmental Fate

Submitted environmental fate data meet the requirements for this screening level assessment with no fate and transport data gaps.

1.5.2 Ecological Effects

The primary uncertainty in the ecological effects data for sulfoxaflor is lack of a reliable Tier 2 semi-field study for assessing impacts on honey bee colony strength and brood development in accordance with OECD-established test guidelines**.** It is further noted that the high variability in sulfoxaflor residues from the cotton residue study and the nature of the cotton flowering introduces uncertainty in the extrapolation of these residue data to other crops. Therefore, additional data on the nature and magnitude of sulfoxaflor residues in one or more pollinator-attractive crops would be needed to address this source of uncertainty. Other uncertainties include lack of definitive toxicity endpoints for passerine birds and larval honey bees.

2. PROBLEM FORMULATION

Problem formulation provides a strategic framework for the risk assessment. It sets the objectives for the risk assessment and provides a plan for analyzing the data and characterizing the risk (US EPA 1998). By identifying the important components of the risk assessment process, it focuses the assessment on the most relevant ecological receptors (species), chemical properties, exposure routes, and endpoints. The structure of this risk assessment is based on guidance contained in U.S. EPA's *Guidance for Ecological Risk Assessment* (USEPA 1998) and is consistent with procedures and methodology outlined in the Overview Document (USEPA 2004).

2.1 Nature of the Regulatory action

The purpose of this assessment is to evaluate the environmental fate and ecological risks for the proposed new registration of the chemical sulfoxaflor. Under Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), U.S. EPA is required to evaluate the potential of new pesticides (and new pesticide uses) to cause adverse effects to the environment. Potential effects to listed species (species on the Federal list of endangered and threatened wildlife and plants) are also considered under the Endangered Species Act in order to ensure that the registration of sulfoxaflor is not likely to jeopardize the continued existence of such listed species or adversely modify their habitat. To these ends, this assessment follows U.S. EPA's guidance on conducting ecological risk assessments and policies for assessing risk to non-target and listed organisms (U.S. EPA, 1998 and U.S. EPA, 2004).

2.2 Nature of the Chemical Stressor

2.2.1 Overview of Pesticide Usage

Sulfoxaflor is proposed for application as a liquid spray applied by ground and aircraft equipment on a variety of crops including beans, berries, canola, citrus, fruits (pome/stone), ornamentals, grains "small", soybeans, tree nuts, turf, vegetables (brassica "leafy" bulb, cucurbits, fruity including okra, leafy, and root & tuber) and watercress. Sulfoxaflor is to be applied to watercress foliage growing in beds completely drained prior to, during and after the application. Aphids appear to be the main target pests for watercress. Given the fact that watercress is harvested for its foliage and mostly propagated by vegetative parts, it is not expected that the chemical will be applied during bloom except in beds used for seed production.

2.2.2 Pesticide Type, Class, and Mode of Action

Sulfoxaflor is a new class of insecticide as it is currently the only member of the sulfoxamine subclass of the neonicotinoid insecticides according to the Insecticide Resistance Action Committee (IRAC).[2] Other subclasses of neonicotinoid insecticides include the cyano-substituted (*e.g.*, acetamiprid and thiacloprid) and the nitroguanidine-substituted neonicotinoids (*e.g.*, imidacloprid, thiamethoxam, clothianidin and dinotefuran) Its common mode of action (MOA) as a neonicotinoid is that of an agonist of the nicotinic acetylcholine receptor (nAChR) whereby it exhibits excitatory responses including tremors, followed by paralysis and mortality in target insects (Zhu *et al.* 2011). Sulfoxaflor has also not demonstrated cross-resistance in strains of whitefly and brown planthopper that were bred to be highly resistant to the nitroguanidine subclass neonicotinoid such as imidacloprid (Babcock *et al.* 2010; Zhu *et al.* 2011); this lack of cross resistance is believed to be partially due to sulfoxaflor's lack of susceptibility to the metabolic mechanisms that are considered responsible for insect resistance to neonicotinoids (*e.g.*, upregulation of monooxygenase [CYP6G1] enzymes). Zhu *et al.* also indicate the specific nature sulfoxaflor binding to the nAChR likely differs from that of other neonicotinoid subclasses. As a result, the IRAC classifies sulfoxaflor in its own subclass (subclass C; sulfoxamines) under Group 4 (nicotinic acetylcholine receptor agonists), whereas nitroguanidine-substituted neonicotinoids such as imidacloprid, acetamiprid and thiamethoxam are in subclass A.

2.2.3 Overview of Physicochemical, Fate, and Transport Properties

Sulfoxaflor is characterized by a water solubility ranging from 550 to 1,380 ppm with low potential for volatilization from dry and wet surfaces. Partitioning coefficient of sulfoxaflor from octanol to water (K_{ow}) suggests low potential for bioaccumulation in aquatic organisms such as fish. According to the registrant, sulfoxaflor is intended to act through both contact action and ingestion and provides both knockdown (symptoms are typically observed within 1-2 hours of application) and residual control (generally provides from 7 to 21 days of residual control).

Sulfoxaflor is a systemic insecticide which displays translaminar movement when applied to foliage. Movement of sulfoxaflor within the plant follows the direction of water transport within the plant (*i.e.,* xylem mobile) as indicated by phosphor translocation studies in several plants including cabbage, pepper and cotton (MRID 48445804). Example phosphor images for cotton from this study are shown in **Figure 1.** From zero to 72 hours, Panel A and B of **Figure 1** indicate little movement of ^{14}C-labeled sulfoxaflor when applied to the cotton leaf (mainly outward to leave edge). In contrast, Panel C and D of **Figure 1** indicate that when sulfoxaflor is applied to the plant stem, it is transported upward to all stem and leaf tissues along the water transpiration stream. Thus, while foliar applications to leaf surfaces would likely result in localised (translaminar) transport, they would also likely involve contact with lower portions of the plant (stems) which would result in 'upward' transport throughout the plant.

[2] http://www.irac-online.org/eClassification/

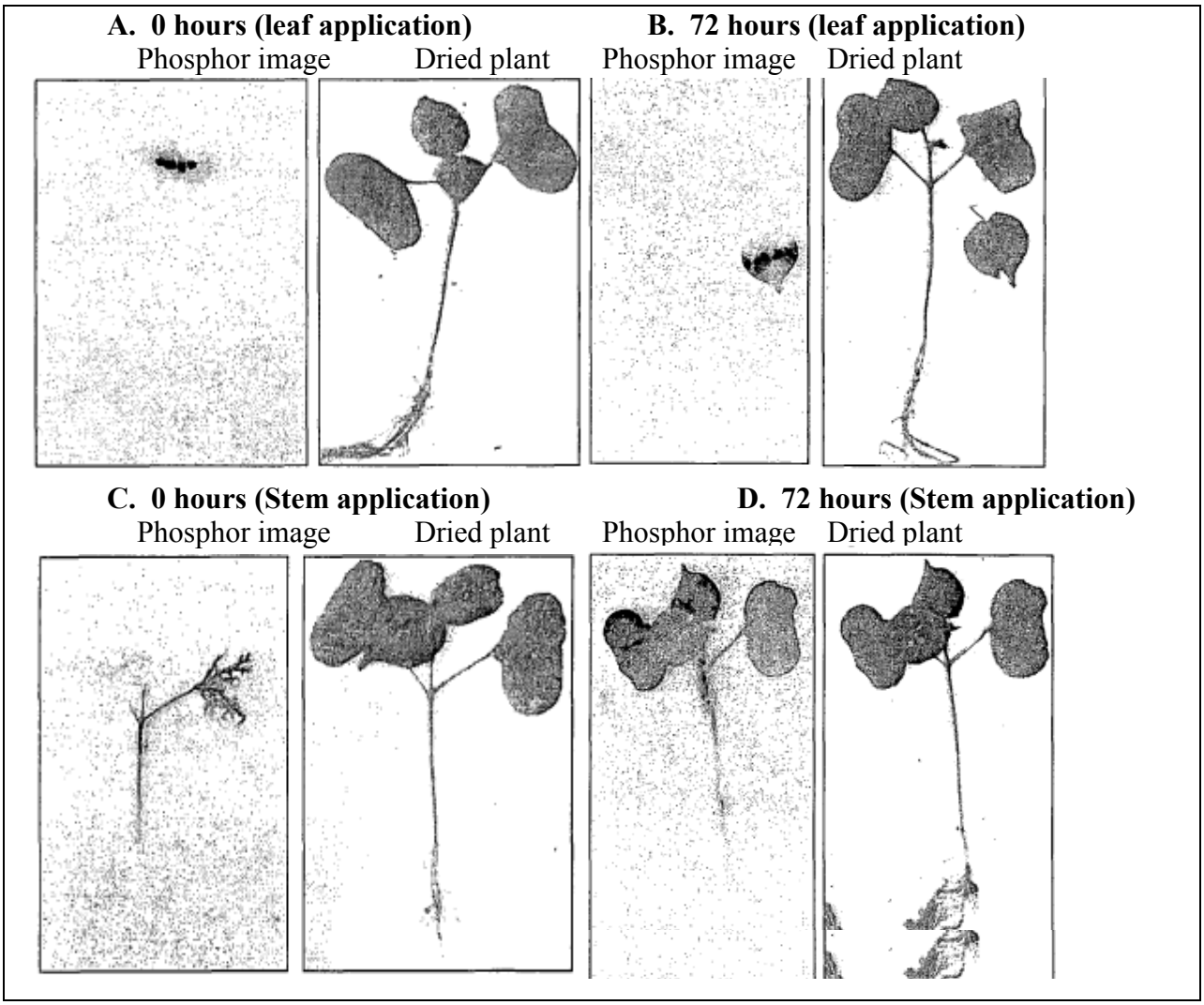


Figure 1. Results from cotton plant translocation study with sulfoxaflor applied to leaf (Panel A&B) and stem (Panel C&D); MRID 48445804

Sulfoxaflor is resistant to hydrolysis and photolysis but transforms quickly in soils. In contrast, sulfoxaflor reaching plant foliage enters into plant tissue and is metabolized into X-474 and X-061. Furthermore, sulfoxaflor reaching aquatic systems by drift is expected to degrade rather slowly.

2.2.4 Stressor Source, Intensity and Identity

Sulfoxaflor is formulated as a suspension concentrate (SC) and water dispersible granules (WDG) and is proposed for application as a liquid spray on variety of crops. It is proposed to be applied to foliage using ground, airblast and/or aerial spray equipments. The maximum single rate of application for sulfoxaflor formulations ranges from 0.043 to 0.133 lb a.i/A with a maximum yearly rates of 0.090 to 0.266 lb a.i/A/year applied in two or three applications at intervals ranging from 5 to 14 days.

In characterizing the nature of this stressor, both exposure and toxicity of the residues of interest (parent, X-474 and X-540) and other degradates are considered for both aquatic and terrestrial systems.

1. Exposure Considerations: For understanding the source and intensity of sulfoxaflor in aquatic systems, a conceptual diagram is used to understand the distribution of expected parent and associated degradates in surface water and ground water (**Figure 2**).

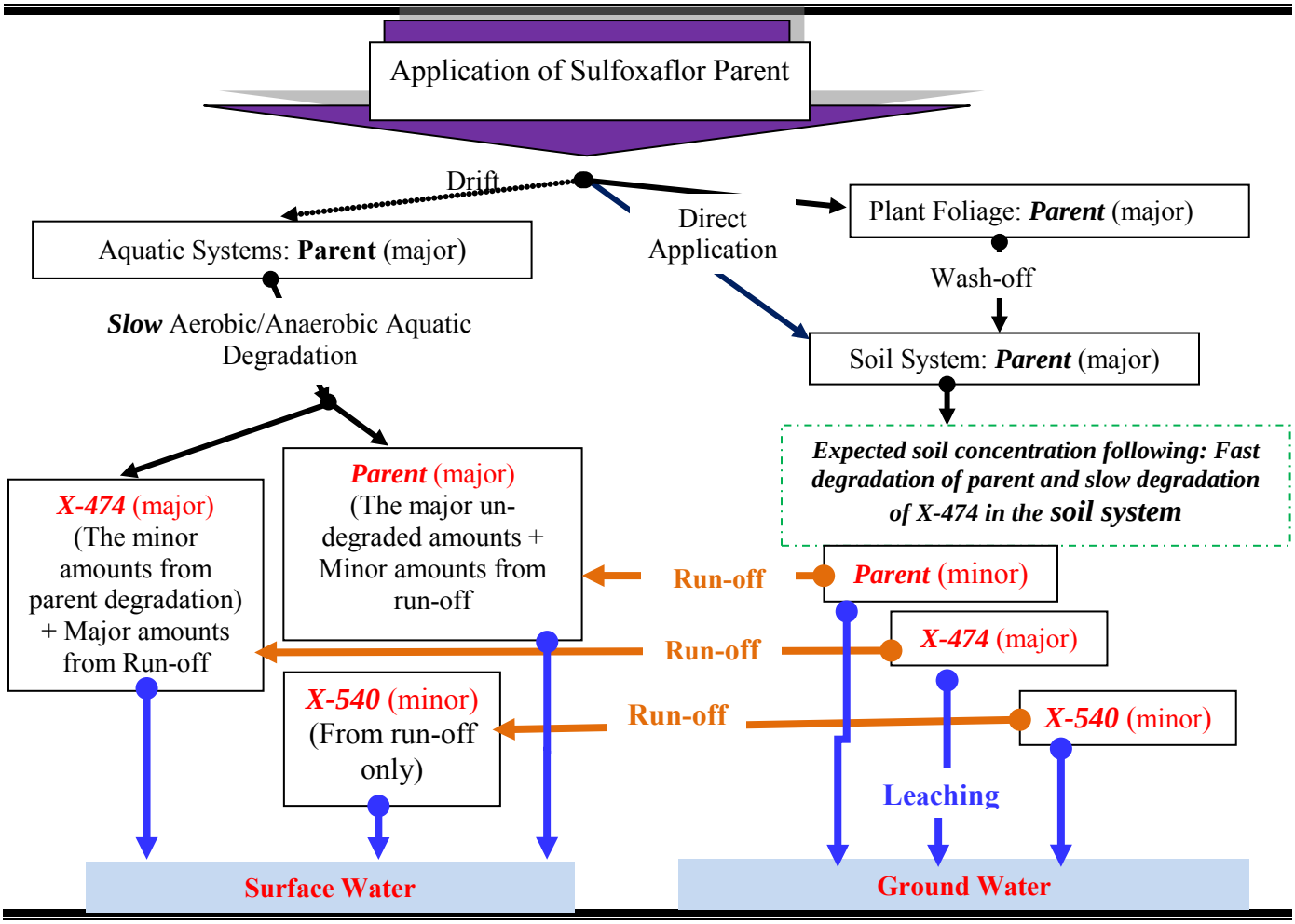


Figure 2. Diagram summarizing distribution of expected residues of interest constituents in surface water and ground water.

As shown in **Figure 2**, the source and intensity of the parent and degradates are expected to be controlled by fate processes dominant in various compartments of the natural environment where the chemicals are expected to reach. These processes include run-off, leaching and spray drift. Partitioning of sulfoxaflor to air is not expected to be important due to the low vapor pressure and Henry's Law constant for sulfoxaflor. Exposure in surface water results from drifted parent as only minor amounts is expected to run-off only when rainfall and/or irrigation immediately follow application. For the degradate **X-**

474, major amounts are expected due to run-off of degraded parent compound in the soil. For the degradate **X-540**, minor amounts are expected from run-off alone.

In terrestrial systems, the source of the pesticide stressor is its foliar application that is expected to mostly reach the foliage and partly reach the soil system as parent. Sulfoxaflor reaching the foliage (including plant stems) is expected to partially move into the plant tissue and degrade over time**.** However, the portion of the parent pesticide that is left on the foliage is expected to stay as parent. The degradate X-474 is also considered relevant to exposure in terrestrial systems, due to biotransformation of parent in soil and subsequent uptake by plants. X-540 is not a major metabolite in plants (observed < 1% of TRR in lettuce metabolism studies and not in all in the other plant metabolism studies).

2. Toxicity Considerations: In aquatic systems, organisms are expected to be exposed to parent sulfoxaflor and the degradation products X-474 and X-540 (**Figure 2).** Comparative toxicity data for one freshwater fish and one freshwater invertebrate species indicate that sulfoxaflor and X-474 are both practically non-toxic on an acute exposure basis (LC_{50} values are all >100 mg a.i/L; See **Section 4** for additional discussion). No chronic toxicity data are available for comparing the toxicity of sulfoxaflor and its degradates to aquatic organisms. Toxicity data for mammals and birds indicate that X-474 is less acutely toxic compared to parent sulfoxaflor, while the minor degradate, X-540, is about 2X more acutely toxic than parent based on mammalian acute LD_{50} data. There is also indication for increased toxicity of X540 compared to parent in a subchronic mammalian dietary study; however, the endpoints quantified (liver weight, mitotic figures) are not quantitatively linked to assessment endpoints used for ecological risk assessment (e.g., survival, growth, reproduction).

For terrestrial organisms, available data indicate that the degradate X-474 is much less toxic than the parent to birds, mammals, and insects (honey bee) on an acute exposure basis (See **Section 4** for details). Furthermore, results from the Health Effects Division assessment of residues of concern indicate the mode of action of sulfoxaflor is not conserved with X-474 (D398294). Regarding the degradate X-061, mammalian acute toxicity data indicate it is about 2X less toxic than the sulfoxaflor parent and practically non-toxic to the honey bee. Although X-540 is more acutely toxic than parent sulfoxaflor to the rat, X-540 is not a major metabolite in plants as indicated above.

3. Stressors of Concern. For aquatic organisms, **the stressor of concern to aquatic organisms is considered to be "sulfoxaflor parent + X-540**, assuming equal toxicity as parent sulfoxaflor. The equal toxicity assumption between parent and X-540 is based on the similarity in their acute oral toxicity to mammals (i.e., within a factor of two). Although X-474 is considered a major degradate, it is not included in the stressor for aquatic organisms because of its lack of acute toxicity, expectation that it does not share the same MOA as parent due to loss of cyano-substitution, and QSAR results indicating its low toxicity.

For terrestrial animals (birds, mammals, and terrestrial invertebrates), **the stressor of concern is defined as parent sulfoxaflor only**. This definition considers the lower

potency of the two primary degradation products in plants (X-474 and X-061) and lack of significant exposure expected for X-540. This stressor definition is also consistent with HED's residue of concern findings for defining residue tolerance values in crops. For terrestrial plants, the stressor is defined as sulfoxaflor only given that no comparative toxicity data for plants are available for the parent or degradates and that parent chemical was not toxic to terrestrial plants at or above the proposed maximum application rates.

2.3 Ecological Receptors

The receptor is the biological entity that is exposed to the stressor (US EPA, 1998). Aquatic receptors potentially at risk include (but are not limited to): fish, amphibians, invertebrates (*e.g.*, aquatic insects, mollusks, crustaceans, and worms), vascular and nonvascular aquatic plants. Terrestrial receptors potentially at risk include (but are not limited to): birds, mammals, reptiles, amphibians, terrestrial invertebrates (*e.g.*, insects, worms, arachnids), and plants.

Consistent with the process described in the Overview Document (US EPA, 2004), this risk assessment uses the surrogate species approach in its evaluation of sulfoxaflor. Toxicological data generated from surrogate test species, that are intended to be representative of broad taxonomic groups, are used to extrapolate to potential effects on a variety of species (receptors) included under these taxonomic groupings.

Acute and chronic toxicity data from studies submitted by pesticide registrants along with the available open literature are used to evaluate potential direct effects of sulfoxaflor to the aquatic and terrestrial receptors identified in this section. Since sulfoxaflor is a new active ingredient, the availability of open literature information on its toxicity is expected to be limited. The open literature studies are identified through EPA's ECOTOX database (http://cfpub.epa.gov/ecotox/), which employs a literature search engine for locating chemical toxicity data for aquatic life, terrestrial plants, and wildlife. The evaluation of both sources of data can also provide insight into the direct and indirect effects of sulfoxaflor on biotic communities due to loss of species that are sensitive to the chemical and changes in structure and functional characteristics of the affected communities.

A summary of the taxonomic groups and the surrogate species tested to help understand potential acute ecological effects of pesticides to non-target species is provided in **Table 2**. In addition, the table provides a preliminary overview of the potential acute toxicity of sulfoxaflor by providing the acute toxicity classifications.

Table 2. Taxonomic Groups, Test Species and Acute Toxicity Classification for Assessing Ecological Risks of Sulfoxaflor to Non-target Organisms

Taxonomic Group	Example(s) of Surrogate Species	Acute Toxicity Classification
Birds[1]	Mallard duck (*Anas platyrhynchos*)	Practically non-toxic
	Bobwhite quail (*Colinus virginianus*)	Slightly toxic
	Zebra finch (*Poephila guttata)*	Moderately toxic
Mammals	Laboratory rat (*Rattus norvegicus*)	Slightly toxic

Taxonomic Group	Example(s) of Surrogate Species	Acute Toxicity Classification
Insects	Honey bee (*Apis mellifera L.*) Bumble bee (*Bombus terrestris*)	Very highly toxic Moderately toxic
Freshwater fish[2]	Bluegill sunfish (*Lepomis macrochirus*) Rainbow trout (*Oncorhynchus mykiss*) Carp (*Cyprinus carpio)*	Practically non-toxic
Freshwater invertebrates	Water flea (*Daphnia magna*)	Practically non-toxic
Estuarine/marine fish	Sheepshead minnow *(Cyprinodon variegatus)*	Practically non-toxic
Estuarine/marine invertebrates	Mysid shrimp *(Americamysis bahia)* Eastern oyster (*Crassostrea virginica)*	Highly toxic Practically-non toxic

[1] In absence of data, birds are used as surrogates for terrestrial-phase amphibians and reptiles.
[2] In absence of data, freshwater fish may be surrogates for aquatic-phase amphibians.

2.4 Ecosystems at Risk

The ecosystems at potential risk from sulfoxaflor are extensive in scope due to the wide geographic distribution of potential sulfoxaflor application sites. In general terms, terrestrial ecosystems potentially at risk could include the treatment areas directly and adjacent areas that may receive drift or runoff. This could include the treatment area itself as well as other cultivated fields, fencerows and hedgerows, meadows, fallow fields or grasslands, woodlands, riparian habitats and other uncultivated areas.

Aquatic ecosystems potentially at risk include water bodies adjacent to (or downstream from) the treatment area and might include impounded bodies such as ponds, lakes, reservoirs and wetland areas, or flowing waterways such as streams and rivers. For uses in coastal areas, aquatic habitat also includes marine ecosystems, including estuaries and salt marshes.

2.5 Assessment Endpoints

Assessment endpoints represent the actual environmental value that is to be protected, defined by an ecological entity (species, community, or other entity) and its attribute or characteristics (US EPA, 1998). For sulfoxaflor, the ecological entities may include the following: birds, mammals, freshwater fish and invertebrates, estuarine/marine fish and invertebrates, terrestrial plants, insects, and aquatic plants and algae. The attributes for each of these entities may include growth, reproduction, and survival and are discussed further in **Section 2.7: (Analysis Plan)**.

2.6 Conceptual Model

For a pesticide to pose an ecological risk, it must reach ecological receptors in biologically significant concentrations. An exposure pathway is the means by which a pesticide moves in the environment from a source to an ecological receptor. For an ecological pathway to be complete, it must have a source, a release mechanism, an environmental transport medium, a point of exposure for ecological receptors, and a feasible route of exposure.

A conceptual model is used in this risk assessment to provide a written and visual description of the predicted relationships between sulfoxaflor, potential routes of exposure, and the predicted effects for the assessment endpoint. A conceptual model consists of two major components: risk hypotheses and a conceptual diagram (US EPA, 1998).

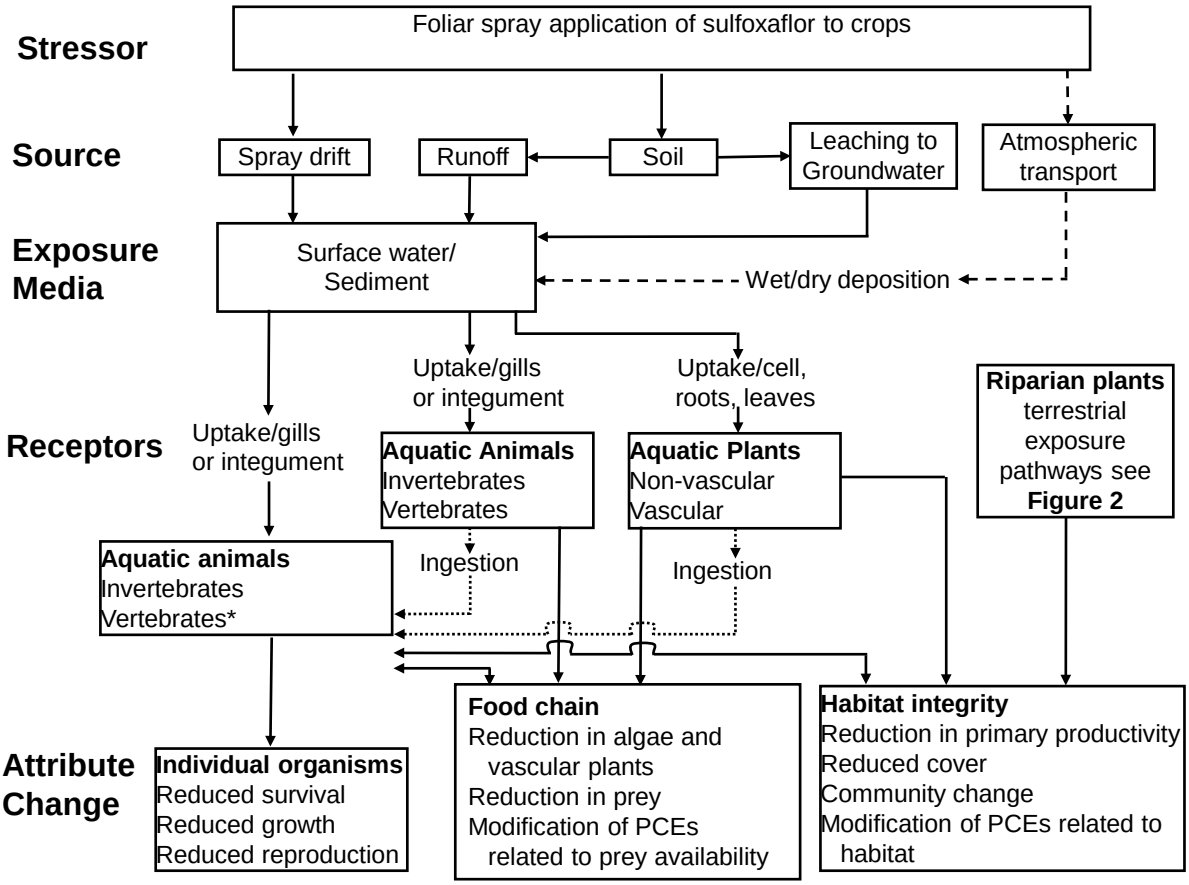
2.6.1 Diagram

Based on the preliminary iterative process of examining fate and effects data, the conceptual model or the risk hypothesis model for spray application to agricultural crops has been established, refined and included in **Figure 3, Figure 4,** and **Figure 5**, respectively. In establishing the diagram for the conceptual model it was necessary to go through an iterative process to identify: (1) likely stressors/exposure pathways and (2) organisms that are most relevant and applicable to this assessment.

Primary exposure routes for aquatic organisms include spray drift and runoff of sulfoxaflor (and its degradates) into nearby bodies of water. Once in the water, the primary exposure route to aquatic organisms is direct uptake across respiratory membranes (animals) and roots/integument (plants). Dietary uptake (ingestion) is not considered an important exposure pathway given the very low bioaccumulation potential of sulfoxaflor.

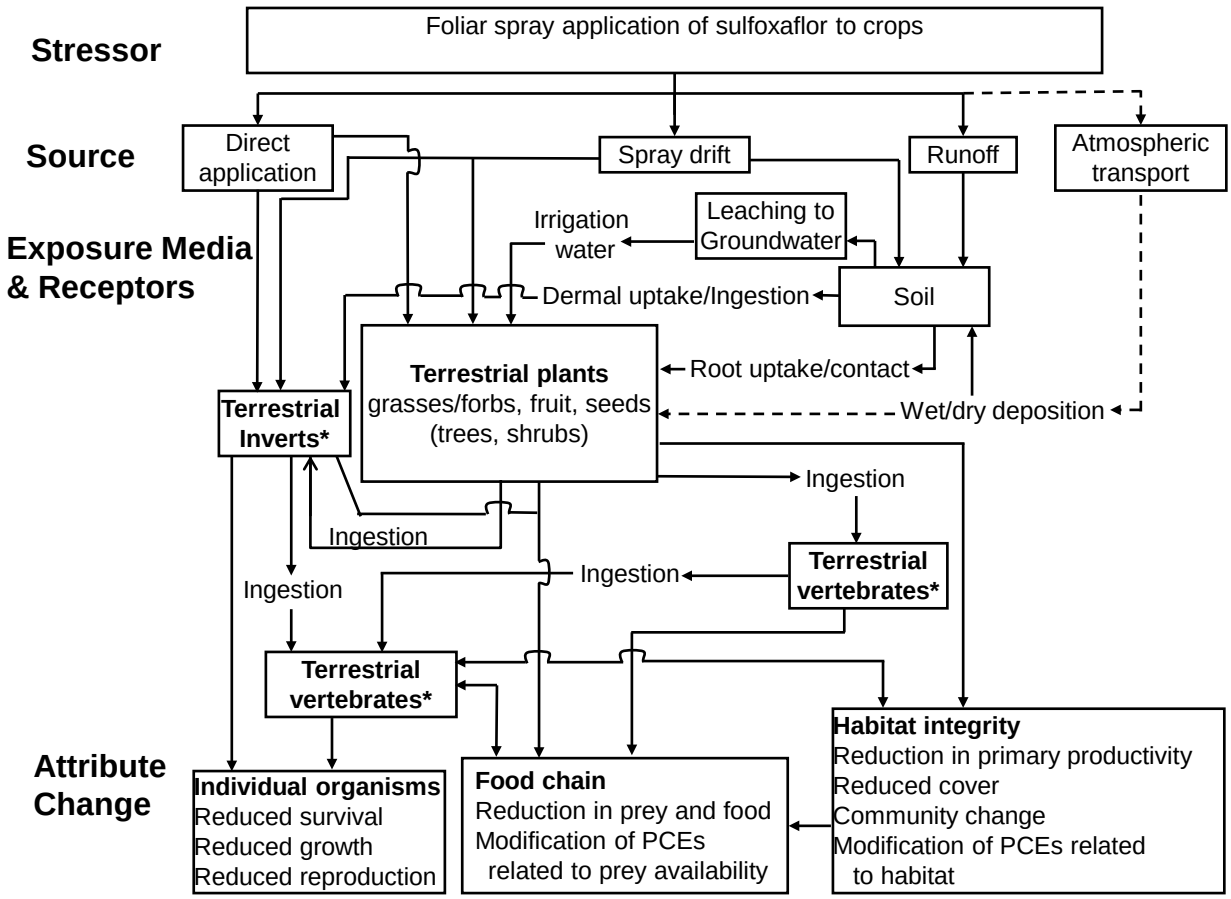
Primary exposure routes for terrestrial organisms (except bees) include direct contact with spray droplets, dermal contact with foliar residues, uptake from soil (plants and soil invertebrates) and consumption of contaminated foliage (herbivorous animals). Inhalation is not considered an exposure route of concern based on results of the Screening Tool for Inhalation Risk (STIR; version 1.0) model (**Appendix E**). Consumption of contaminated drinking water is a potential exposure route of concern based on results of Screening Imbibition Program (SIP; version 1.0; **Appendix E**). However, additional refinements are needed to determine if actual risks result from this exposure pathway. At this time, EFED has does have available an approved modeling tool to enable refinements to the SIP screening model.

For managed bees (e.g., honey bees), the primary exposure routes of concern include direct contact with spray droplets, dermal contact with foliar residues, and ingestion through consumption of contaminated pollen, nectar and associated processed food provisions (*e.g.,* brood food, royal jelly, propolis). Exposure of hive bees via contaminated wax is also possible, although difficult to quantify at this time. Exposure of bees through contaminated drinking water is not expected to be nearly as important as exposure through direct contact or pollen and nectar (USEPA, 2012).



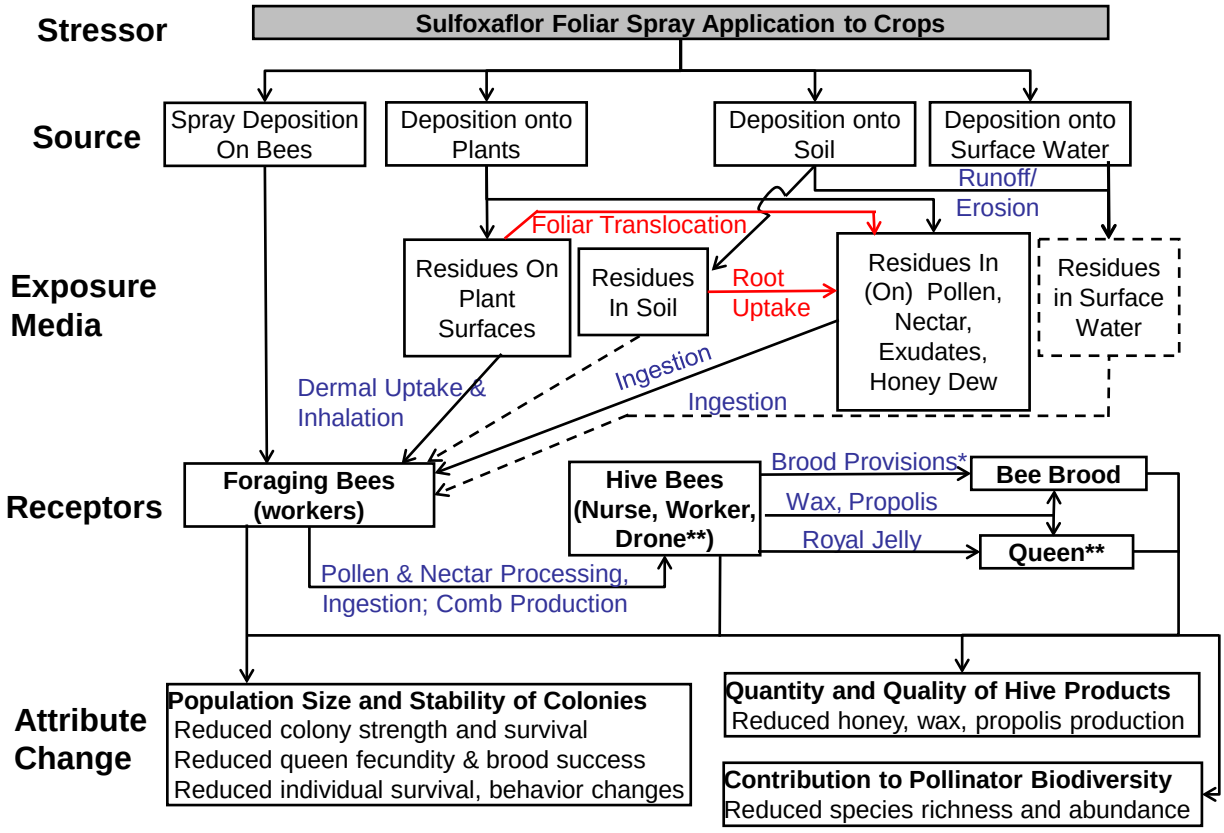
* Exposure of piscivorous wildlife via ingestion of aquatic organisms is not an exposure pathway of concern for sulfoxaflor

Figure 3. An ecological conceptual model for aquatic exposure from spray application of sulfoxaflor



* See **Figure 3** for a detailed conceptual model of sulfoxaflor risks to honey bees.

Figure 4. An ecological conceptual model for terrestrial exposure from spray application of sulfoxaflor



* Brood initially rely on brood jelly and royal jelly, but later in development consume processed pollen and honey; whereas queens rely solely on royal jelly.
** interception of spray droplets is also a potential route of exposure during mating and orientation flights

Figure 5. An ecological conceptual model for honey bee exposure from spray application of sulfoxaflor

2.6.2 Risk Hypothesis

Risk hypotheses are specific assumptions about potential adverse effects (*i.e.*, changes in assessment endpoints) and may be based on theory and logic, empirical data, mathematical models, or probability models (EPA 1998). The ensuing risk assessment will evaluate whether or not the specific risk hypotheses are supported. For foliar applications of sulfoxaflor, the following ecological risk hypothesis is being employed for this risk assessment:

> *Based on the environmental fate, systemic uptake and distribution by plants and nature of foliar applications of sulfoxaflor to crops, (including its primary degradates of concern), there is a potential that terrestrial and/or aquatic organisms will be exposed when sulfoxaflor is used in accordance with the label. Consequently, considering the MOA and toxicity of sulfoxaflor, the proposed uses of sulfoxaflor have the potential to cause adverse effects upon the survival, growth, and reproduction of non-target terrestrial and aquatic plants and animals.*

2.7 Analysis Plan

2.7.1 Methods for Conducting Ecological Risk Assessment

The primary method used to assess risk in this screening-level assessment is the risk quotient (RQ) and follows closely methods outlined in the EPA Overview Document (USEPA, 2004). The RQ is the risk value for the screening-level assessment and is the result of comparing measures of exposure to measures of effect. A commonly used measure of exposure is the estimated exposure concentration (EEC) and commonly used measures of effect include toxicity values such as the median lethal dose to 50% of the organisms tested (LD_{50}), medial lethal concentration to 50% of tested organisms (LC_{50}), the no observed adverse effect level (NOAEL)[3], and the no observed adverse effect concentration (NOAEC). The resulting ratio of the point estimate of exposure and the point estimate of toxicity, i.e., the RQ, is then compared to a specified level of concern (LOC), which represents a threshold for concern; if the RQ exceeds the LOC, risks concerns are triggered. Risk presumptions, along with the corresponding RQs, equations, and LOCs are summarized in
Section 5.

Generation of robust RQs is dependent on the quality of data from both fate and toxicological studies. The adequacy of the submitted data was evaluated relative to Agency guidelines. The following identified data gaps for ecological fate and toxicity endpoints result in a degree of uncertainty in evaluating the ecological risk of sulfoxaflor.

[3] A NOAEL refers to a dose-based toxicity endpoint whereas a NOAEC refers to a concentration based endpoint.

2.7.2 Measures of Exposure

Measures of exposure are estimates of exposure for a receptor determined by modeling or monitoring data. Measures of exposure for sulfoxaflor, in this assessment, are obtained from modeling efforts only, since this is a new chemical and national-scale monitoring data are not expected to be present. Exposure models used for this assessment include the suite of standard exposure models commonly used in pesticide risk assessments (USEPA, 2004). Generally, aquatic exposure estimates are generated from EPA models and incorporate maximum proposed use rates, minimum application intervals, and empirically-derived fate properties. Further details of the exposure models can be found in the Exposure Characterization section of the risk assessment and on the web.

http://www.epa.gov/oppefed1/models/water/index.htm

Exposure to aquatic organisms is assumed to occur through direct contact with surface water contaminated by drift and/or runoff/erosion from agricultural fields. Aquatic exposure concentrations, for all crops except watercress, in this assessment were based on EECs calculated using Tier II-linked Pesticide Root Zone Model (version 3.12.2 Carousel *et al.*, 2005) and the Exposure Analysis Modeling System (version 2.98.04; Burns, 1997) referred to as PRZM/EXAMS. Model runs were executed using graphic interface (EXPRESS or PE-5). For watercress, EECs were conservatively estimated using the Tier 1 Rice Model.

Measures of exposure for terrestrial mammals, birds, reptiles and amphibians similarly incorporate maximum proposed use rates, but rely less on environmental fate properties. Terrestrial exposures were estimated using a number of methods. The Kenaga nomogram, as modified by Fletcher *et al*., (Kenaga and Hoerger 1972; Fletcher *et al*. 1994) is used to relate pesticide application rates to chemical residues on terrestrial food items. The surface residue concentration (in parts per million; ppm) is estimated by multiplying the application rate (pounds active ingredient per acre; lbs a.i./A) by a value specific to each food item. For numerous applications for a given use, the Terrestrial Exposure (T-REX; version 1.5.1) model is used with the maximum application rates and minimum application intervals allowable on the proposed labels. Degradation is considered using a first-order decay rate dependent on a chemical-specific foliar dissipation half-life of 12.3 days for sulfoxaflor based on submitted residue-decline data. The conceptual approach taken to estimate residues (upper-bound and mean) in potential dietary sources for mammals and birds is presented in the model T-REX Version 1.5.1 available at:

http://www.epa.gov/oppefed1/models/terrestrial/index.htm

Exposure of non-target terrestrial and semi-aquatic plants to sulfoxaflor is estimated using the TerrPlant model (version 1.2.2) which accounts for both spray drift and runoff as a function of application rate.

Exposure of honey bees to sulfoxaflor is estimated using a Tiered approach as outlined in USEPA (2012): *Draft Framework for Pollinator Risk Assessment*[4]. Tier 1 of this draft framework involves estimating pesticide doses to honey bees from direct contact using an upper-bound estimate of 2.7 µg a.i/bee per 1 lb a.i/A and an upper-bound estimate of oral ingestion using the T-REX model for arthropod residues. Further refinement of the oral doses is conducted using available measured pesticide residue information for pollen and nectar. Additional information on estimation of oral and contact doses to honey bees is provided in **Appendix D.**

2.7.3 Measures of Effect

Measures of ecological effects are obtained from a suite of registrant-submitted guideline studies conducted with a limited number of surrogate species. The test species are not intended to be representative of the most sensitive species but rather were selected based on their ability to thrive under laboratory conditions. Measures of effect are based on deleterious changes in an organism as a result of chemical exposure. Functionally, measures of effect typically used in risk assessments include changes in survival, reproduction, or growth as determined from standard laboratory toxicity tests. The focus on these effects for quantitative risk assessment is due to their clear relationship to higher-order ecological systems such as populations, communities, and ecosystems. Although monitoring data such as adverse effect incident reports may also be used to provide supporting lines of evidence for the risk characterization, monitoring data are lacking for this new chemical. Over the 2012 growing season, a Section 18 emergency use was granted for application of sulfoxaflor to cotton in four states (MS, LA, AR, TN). To date, no incident reports have been received in association with the use of sulfoxaflor. However, due to the nature of ecological incident reporting, absence of incidents cannot be construed with absence of incidents. In addition, effects other than survival, reproduction, and growth may be considered, rarely are they used quantitatively to estimate risks since, in many cases, the relationship between these effects and higher-order processes is tenuous at best. Commonly used laboratory-derived toxicity values include estimates of acute mortality (*e.g.*, LD_{50}, LC_{50}) and estimates of effects due to longer term, chronic exposures (*e.g.*, NOAEC, NOAEL). The latter can reflect changes seen in mortality, reproduction, or growth. In general, for a given assessment endpoint the lowest (*i.e.*, most sensitive) relevant measure of effect is used is calculating the RQ. In addition, for insect pollinators (honey bee), effects are also assessed at the colony level using semi-field and/or full-field studies. Measurement endpoints include colony strength, foraging activity, forager mortality, and various measures of brood development.

Assessment endpoints and their respective measures of effect are listed in **Table 3**.

[4] http://www.epa.gov/scipoly/sap/meetings/2012/091112meeting.html

Table 3. Summary of assessment and measurement endpoints for Sulfoxaflor

Assessment Endpoint	Measures of Exposure	Measures of Effect
1. Abundance (i.e., survival, reproduction, and growth) of individuals and populations of birds[2].	Maximum (peak) residues on food items (foliar)	1a. Zebra finch and mallard duck acute oral LD_{50}. 1b. Mallard duck subacute dietary LC_{50}. 1c. Mallard duck and bobwhite quail chronic reproduction NOAEC and LOAEC.
2. Abundance (i.e., survival, reproduction, and growth) of individuals and populations of mammals.	Maximum (peak) residues on food items (foliar)	2a. Laboratory rat and mouse acute oral LD_{50}. 2b. Laboratory rat 2-generation reproduction chronic NOAEL and LOAEL.
3. Survival and reproduction of individuals and communities of freshwater fish[3] and invertebrates.	Peak EEC (acute), 21-d & 60-d surface water EEC (chronic)[1]	3a. Rainbow trout, bluegill sunfish and carp acute LC_{50}. 3b. Fathead minnow early life stage NOAEC and LOAEC. 3c. Daphnid acute EC_{50}. 3d. Daphnid chronic reproduction NOAEC and LOAEC.
4. Survival and reproduction of individuals and communities of estuarine/marine fish and invertebrates.	Peak EEC (acute), 21-d & 60-d surface water EEC (chronic)[1]	4a. Sheepshead minnow acute LC_{50}. 4b. Saltwater mysid acute LC_{50}.
5. Survival of individuals and communities of freshwater and estuarine/marine benthic organisms.	21-d pore water and sediment EEC[1]	5a. Freshwater midge subchronic NOAEC and LOAEC. 5b. Estuarine/marine mollusk acute EC_{50} based on shell deposition.
6. Perpetuation of individuals and populations of non-target terrestrial plant species.	Estimates of runoff and spray drift to non-target areas	6a. Monocot and dicot seedling emergence and vegetative vigor EC_{25} values.
7. Maintenance and growth of individuals and populations of aquatic vascular and nonvascular plants.	Peak surface water EEC	7a. *Lemna gibba* acute EC_{50} values based on yield and growth rate. 7b. Algal acute EC_{50} values based on cell density, biomass and growth rate.
8. Population size and stability of managed bee colonies; Quality of hive products	Upper bound oral and contact dose to adult and larvae (laboratory studies)	8a. Honey bee adult acute contact LD_{50}. 8b. Honey bee adult acute oral LC_{50}. 8c. Honey bee larval chronic NOAEC or LD_{10} 8d. Honey bee colony level effects

Assessment Endpoint	Measures of Exposure	Measures of Effect
LD_{50} = Lethal dose to 50% of the test population; NOAEC = No-observed-adverse-effect level; LOAEC = Lowest-observed-adverse-effect level; LC_{50} = Lethal concentration to 50% of the test population; EC_{50}/EC_{25} = Effect concentration to 50/25% of the test population. [1] Based on a 1-in-10-year return frequency. [2] According to EFED risk assessment guidance, birds may be used as surrogates for amphibians (terrestrial phase) and reptiles. [3] According to EFED risk assessment guidance, freshwater fish may be used as surrogates for amphibians (aquatic phase).		

3. ANALYSIS

3.1 Use Characterization

Sulfoxaflor is proposed to be widely used in the U.S. to control or suppress a wide range of insect pests including aphids, plant bugs, stink bugs, whiteflies and certain scales, thrips and psyllids. The list of the proposed crop uses include barley, Brassica (cole) leafy vegetables, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables (except *Brassica*), leaves of root and tuber vegetables, low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, root and tuber vegetables, small fruit vine climbing (except fuzzy kiwifruit), soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turf grass, watercress, and wheat. Sulfoxaflor is formulated as a suspension concentrate "SC" (Proposed label: GF-2032 SC containing 2 lb a.i/gal) and as water dispersible granule "WG" (Proposed label: GF-2372 WG or Transform™ WG containing 50% a.i by weight. Formulations are proposed to be applied as liquid spray by ground, airblast, and aerial into the crop foliage. The potential usage areas may be inferred from the proposed crop use patterns. The spatial extent of usage areas is expected cover large acreages of the proposed crop land in the U.S. **Table 4** contains a summary of all crops proposed to be treated with sulfoxaflor.

Table 4. Crop use patterns proposed for sulfoxaflor; Ground or aerial for all uses except for turf and non-commercial ornamentals (ground application)*

*Crop/Crop Group***	*Crop Group(CG) Or Subgroup (SG)*	*Max Single Rate (lb a.i./A)*	*Max No. of Applications*	*Max Yearly Rate (lb a.i./A)*	*Min Intervals (days)*
Beans	Beans	0.090	3	0.266	7
Berries	SG 13-07F &G	0.090	3	0.266	7
Canola (Rapeseed)	SG 20A	0.043	2	0.090	14
Citrus	CG 10	0.133	2	0.266	7
Cotton	Cotton	0.090	3	0.266	5
Fruits: Pome	CG 11	0.133	2	0.266	7
Fruits: Stone	CG 12	0.133	2	0.266	7
Grains	Small Grains	0.043	2	0.090	14
Ornamentals	Ornamentals	0.133	2	0.266	7
Soybeans	Soybeans	0.090	3	0.266	7
Tree Nuts	CG 14 & Pistachio	0.133	2	0.266	7
Turf grass	Turf grass	0.133	2	0.266	7
Vegetables: Brassica (cole) leafy	CG 5	0.090	3	0.266	7
Vegetables: Bulb	SG 3-07	0.090	3	0.266	7

*Crop/Crop Group***	*Crop Group(CG) Or Subgroup (SG)*	*Max Single Rate (lb a.i./A)*	*Max No. of Applications*	*Max Yearly Rate (lb a.i./A)*	*Min Intervals (days)*
Vegetables: Cucurbit	CG 9	0.090	3	0.266	7
Vegetables: Fruiting & Okra	CG 8 & Okra	0.090	3	0.266	7
Vegetables: Leafy except Brassica	CG 4	0.090	3	0.266	7
Vegetables: Root & tuber /Leaves	CG 1 & 2	0.090	3	0.266	7
Watercress	Watercress	0.090	3	0.266	7

* from pre-bloom to mature fruits for trees and from seeding to harvest for all others
** For detailed crop listing refer to **Appendix A**

3.2 Exposure Characterization

3.2.1 Environmental Fate and Transport Characterization

3.2.1.1 Physical and chemical properties

The physical and chemical properties of Sulfoxaflor are summarized in **Table 5**. These data indicate that the chemical is characterized by a water solubility ranging from 550 to 1,380 ppm in alkaline to acidic conditions, respectively. Sulfoxaflor has a low potential for volatilization from dry and wet surfaces (vapor pressure= 1.9 x 10^{-8} torr and Henry's Law constant= 1.2 x 10^{-11} atm m^3 $mole^{-1}$, respectively at 25 °C). Partitioning coefficient of sulfoxaflor from octanol to water (K_{ow}) suggests low potential for bioaccumulation in aquatic organisms such as fish. However, the logarithm of its portioning coefficient from octanol to air (Log K_{oa}=10) suggests potential bioaccumulation in terrestrial organisms, but the expected relative availability in air is low because amount expected to partition into air is low (low volatility) and it's half-life in the air is expected to be short (range of 8-16 hours). Furthermore, sulfoxaflor is not expected to partition into the sediment due to low K_{oc}.

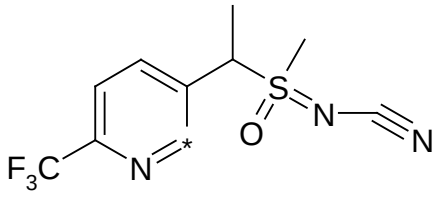
Table 5. Physical and chemical properties of Sulfoxaflor

Property	***Description or Value***	***Reference****
CAS Name	Sulfoxaflor: cyanamide, N-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-lambda 4-sulfanylidene]-	Registrant Data
Molecular Formula	$C_{10}H_{10}F_3N_3OS$	
CAS number	946578-00-3	
PC code	005210	
Molecular Weight	277.27 g/mol	

Property	*Description or Value*	*Reference**
Solubility (mg/L @ 20 C)	**Parent** **X-474** pH 5 → 1,380 mg/L 7,270 mg/L pH 7 → 570 mg/L 7,200 mg/L pH 9 → 550 mg/L 8,480 mg/L In purified water: 670 mg/L 8,090 mg/L	478320-10 478320-23 for X-474
Vapor pressure	Parent 20°C → ≤ 1.1 x 10^{-8} torr; ≤ 1.4 x 10^{-6} Pa; ≤ 1.4 x 10^{-11}atm 25°C → ≤ 1.9 x 10^{-8} torr; ≤ 2.5 x 10^{-6} Pa; ≤ 2.5 x 10^{-11}atm X-474 25°C → ≤ 2.0 x 10^{-9} torr; ≤ 2.7 x 10^{-7} Pa; ≤ 2.7 x 10^{-12}atm	478320-06 478320-22 for X-474
Henry's Law Constant (@ 20 & 25 C)	6.7 x 10^{-12} atm m^3 $mole^{-1}$; 5.1 x 10^{-9} torr m^3 $mole^{-1}$ 1.2 x 10^{-11} atm m^3 $mole^{-1}$; 9.1 x 10^{-9} torr m^3 $mole^{-1}$	478320-07 from VP at 20°C Calculated from VP at 25°C
Half-life in Air ($t_{½}$ in hours)	range: 7.8 - 15.5	EPI-Suit v3.2 (AOPWIN) & Level III Fugacity Model
Log K_{oa}	10.11	EPI-Suit v3.2 (KOAWIN)
K_{ow} @ 20 C & pH 7	Parent: 6 (Log K_{ow} = 0.802) X-474, X-540 and X-457: <2 (Log K_{ow} = 0.3)	478320-11 478320-20/24/27
K_{oc}	7 – 74 mL/g	

3.2.1.2 Fate and Transport Properties

The fate and transport behaviour of Sulfoxaflor had been investigated in a series of laboratory and field studies. The submitted laboratory studies were all conducted with ^{14}C-labelled active substance in the pyridine ring as shown in **Figure 6**.



* denotes position of radiolabel in the pyridine ring

^{14}C-Sulfoxaflor (or XDE-2208)

Figure 6. Radiolabeled sulfoxaflor used in fate and transport studies

Sulfoxaflor consists of two diastereomers in a ratio of approximately 50:50. Each of the diastereomers consists of two enantiomers that cannot be resolved using conventional (non-chiral) high pressure liquid chromatography (HPLC) columns.

a) Abiotic Degradation

Results indicate that hydrolysis, and both aqueous and soil photolysis are not expected to be important in sulfoxaflor dissipation in the natural environment. The fate properties of sulfoxaflor parent and major degradate X-474 in abiotic systems are summarized in **Table 6**. In a hydrolysis study, the parent was shown to be stable in acidic/neutral/alkaline sterilized aqueous buffered solutions (pH values of 5, 7 and 9; MRID 47832-149). In addition, parent chemical as well as its major degradate, were shown to degrade relatively slowly by aqueous photolysis in sterile and natural pond water (t½= 261 to >1,000 days; MRID 478322-83/84). Furthermore, sulfoxaflor was stable to photolysis on soil surfaces (MRID 478320-21).

Table 6. Fate properties of sulfoxaflor parent and its major degradate X-474 in abiotic systems

Property	***Description or Value & Other Relevant Information***	***Reference (MRID)***
Hydrolysis half-life @ 25 °C	**Parent:** **Stable** in sterile aqueous buffered solution at pH values of 5, 7 and 9 **X474 degradate** (no study; results inferred from the dark controls of the aqueous photolysis study (MRID 478322-83): **Stable** in sterile aqueous buffered solution at pH7	478321-49
Environmentally relevant Aqueous photolysis half-lives @ 25 °C; 40° N latitude in summer sunlight	**Parent:** **>1,000 days** in sterile aqueous buffered solution at pH 7.0 **637 days** in natural pond water, Italy; buffered at pH 8.2 **Major degradates: None** **Minor degradates:** X-061 [1-[6-(trifluoromethyl)(2-14C)pyridin-3-yl]ethanol] with a maximum of 2.5% @ study termination (day 14) **(Note: Transformation products was not tracked for the natural pond water samples, transformation products data above are for sterile/buffered water only)** **X-474 degradate:** **261 days** in sterile aqueous buffered solution at pH 7 **>1,000 days** in natural pond water, Italy; buffered at pH 8.2 **Major degradates: None** **Minor degradate:** X-061 (maximum 4.4% at study termination) and X-922 [1-(6-trifluoromethyl-pyridine-3-yl) ethanone] with a maximum of 8.6% at study termination (day 14)	Sterile Water Study: 478322-83 Natural water study: 478322-84
Soil photolysis half-life	**Stable**	478320-21

b) Biotic Degradation

The fate properties of sulfoxaflor and its major degradation product X-474, in biotic systems, are summarized in **Table 7**. In addition, **Table 8** contains a summary for the degradation products observed following parent degradation in various systems. Expected environmental degradation pathways and transformation profiles for Sulfoxaflor are also presented in **Figure 7**.

Based on these data, sulfoxaflor is expected to biodegrade rapidly in aerobic soil (half-lives <1 day). Under aerobic aquatic conditions, biodegradation proceeded at a more moderate rate with half-lives ranging from 37 to 88 days. The major degrade formed in aerobic soil/aquatic systems is X-474. Under anaerobic soil conditions, the parent compound was metabolized with half-lives of 113 to 120 days while under anaerobic aquatic conditions the chemical was more persistent with half-lives of 103 to 382 days.

In contrast to its short-lived parent, the major degradate X-474 is expected to be more persistent than its parent in aerobic/anaerobic aquatic systems and some aerobic soils. In other soils, less persistence is expected due to mineralization to CO_2 or the formation of other minor degradates.

Table 7. Fate properties of sulfoxaflor parent and major degradate X-474 in biotic systems

Property	*Soil or Water/Sediment System**	*Half-life & (Fitting Equation)*		*Reference (MRID)*
		Parent t½	*X-464 t½*	
Aerobic Soil Metabolism (days): 25 °C/ 75% of the water holding capacity (**WHC**)	Lenawee light clay, Michigan, USA: CL	**0.3**	**>1000**	478655-78
	Pullman light clay, Texas, USA: CL	**0.4**	**>1000**	
	Fayette clay loam, Iowa, USA: L	**0.6**	**>1000**	
	Slagle clay loam, Virginia, USA: SL	**0.5**	**>1000**	
Aerobic Soil Metabolism (days): EU Soils incubated for 4 months at 20 °C/ 40% of the **WHC**	Cranwell Series (Site I), Lincolnshire, UK: LS	**<0.1**	**203**	478320-13
	Aberford Series (Site J1), Rutland, UK : L	**<0.1**	**85**	
	Malham Series (Site E), Derbyshire, UK: SL	**<0.1**	**381**	
	LUFA 5M, Kreis Rheim-Pfalz, Germany: SL	**<0.3**	**251**	
Aerobic Soil Metabolism (days)	Aberford Series (Site J1), Rutland, UK : L; EU Soil incubated for 4 months at 10 °C/40% **WHC**	**<1**	**184**	478320-13
Aerobic Soil Metabolism (days):	Aberford Series (Site J1), Rutland, UK : L; EU Soil sterilized/incubated for 4 months at 20 °C/ 40% of the **WHC**	**<1**	**NC**	478320-13
Soil Metabolism: Aerobic Phase (days)	CL Soil, Texas: 8 hrs under aerobic conditions then 113 d under anaerobic conditions @ 25 °C/35% of the **WHC**	**NC**	**NC**	478322-79
Anaerobic phase (days)		**NC**	**320**	
Soil Metabolism: Aerobic Phase (days)	Aberford Series (Site J1), Rutland, UK : L; 2 hrs under aerobic conditions & 120 d under anaerobic conditions @ 25 °C/40% of the **WHC**	**NC**	**NC**	478320-13
Anaerobic phase (days)		**NC**	**532**	
Aerobic Aquatic Metabolism (days for the total system): Pond water/sediment system, Derbyshire, UK (**system-1**)*	**Water:** pH 6.7 and dissolved organic carbon 6.2 ppm) and **Sediment:** sand (pH 6.3 and organic carbon 0.6%) incubated for 103 d @ 20 °C	**88**	**NC**	478320-14

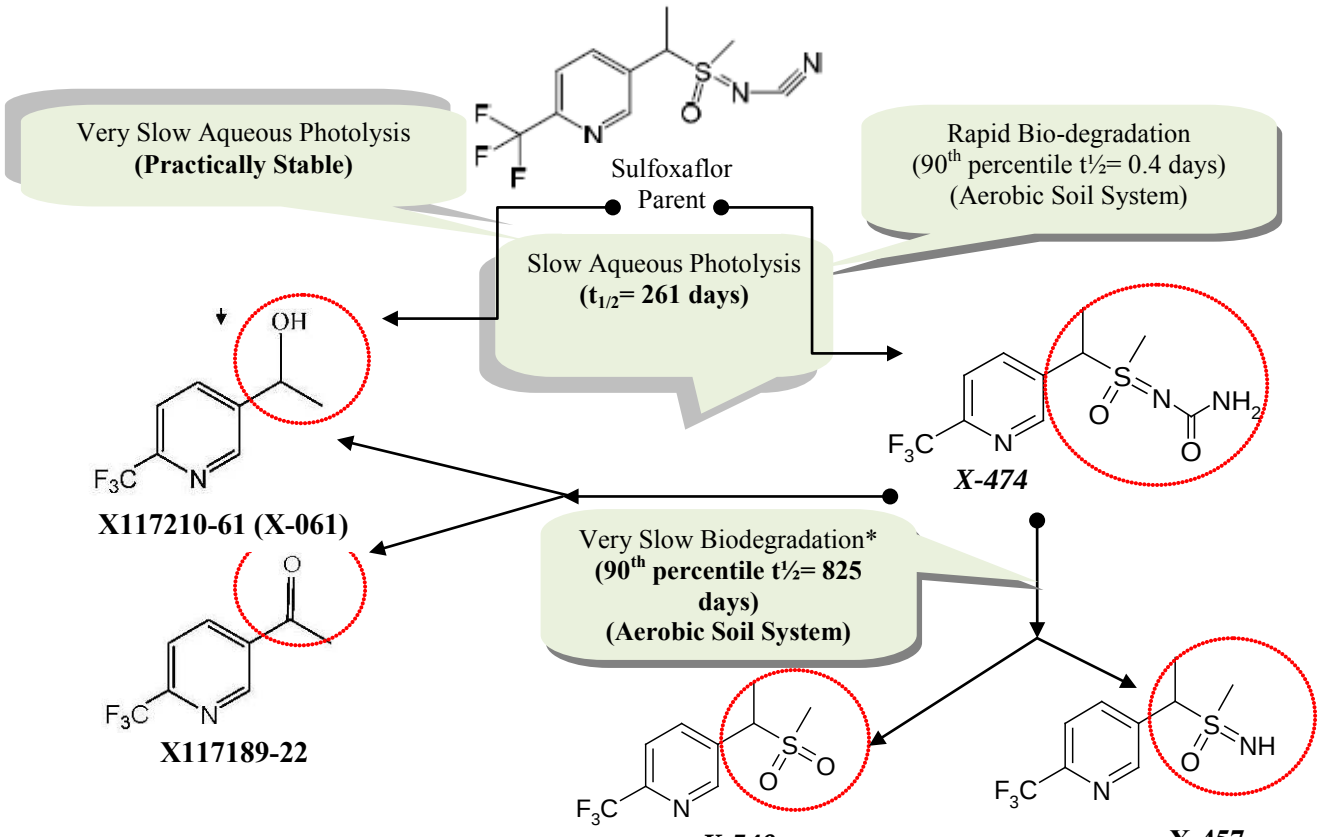
Property	*Soil or Water/Sediment System**	*Half-life & (Fitting Equation)*		*Reference (MRID)*
		Parent t½	*X-464 t½*	
Aerobic Aquatic Metabolism (days for the total system): Pond water/sediment system, Staffordshire, UK (**system-2**)*	**Water:** pH 7.8 and dissolved organic carbon 6.5 ppm) and **Sediment:** silt loam (pH 7.8 and organic carbon 3.9%) incubated for 103 d @ 20 °C	**37**	**NC**	
Anaerobic Aquatic Metabolism (days for the total system): Pond water/ sediment system, VA (**system-3**)*	**Water:** pH 7.5 and dissolved organic carbon 10.0 ppm) and **Sediment:** sand (pH 4.9 and organic carbon 0.2% incubated for 100 d @ 25 °C	**382**	**5,270**	
Anaerobic Aquatic Metabolism (days for the total system): Pond water/ sediment system, IA (**system-4**)*	**Water:** pH 7.8 and dissolved organic carbon 6.7 ppm) and **Sediment:** sandy clay loam (pH 7.3 and organic carbon 1.4%) incubated for 100 d @ 25 °C	**103**	**1,090**	473723-11

*** Abbreviations: NC**= Cannot be calculated due to gain or only few points is available; **Soil Textural Classes: CL**= Clay Loam; **L**= Loam Soil; **SL**= Sandy Loam Soil; and **LS**= Loamy sand; Data for aerobic systems from parent study while that for anaerobic systems from two separate studies: one for parent and the other for the major degradate X-474

Table 8. Parent degradation products for systems described in Table 7, above

Property	*Soil or Water/Sediment System*	*Parent Degradation Products (% of Applied)*	*Reference (MRID)*
Aerobic Soil Metabolism US soils @ 25 °C/ 75% of the **WHC**	Lenawee light clay, MI Pullman light clay, TX Fayette clay loam, IA Slagle clay loam, VA	**Major (MAJ): X-474** (max. 98 to 99% by 14 to 31 days then decreased to 83-90% @ termination); **Minor (MIN):** None; **Mineralization (MRL): CO_2** (max. 1-3% @ termination); **Non-extractable residues (NER):** max. 7-13% @ termination	478655-78
Aerobic Soil Metabolism EU Soils @ 20 °C/ 40% of the **WHC**	Cranwell Series, UK Aberford Series, UK Malham Series, UK LUFA 5M, Germany	**MAJ: X-474** (max. 100% by day 1then decreased to 35-79% @ termination), and **X115795-40** (from 0 to 12%, formation time was variable "ranged from 4 to 81 days after incubation" with no clear decline; Data suggest net gain @ termination); **MIN: X115794-57**(from 0 to 9%, formation time was variable "ranged from 3 to 32 days after incubation" with no clear decline; Data suggest net gain @ termination); **MRL: CO_2** (max. 5-9% @ termination in all soils except Aberford Series with a max. of 28 to 32%); **NER:** max. 4-8% @ termination	478320-13
Aerobic Soil Metabolism	Aberford Series (Site J1), UK @ 10 °C/ 40% of the **WHC**	**MAJ:** X-474 (max. 97% within one day then declined to 68% @ termination); **MIN: X115794-57** (Max. 8% in 62 days decreasing to only 7% within the period from day 90 to termination); and **X115795-40** (Max. 8% within the period from 62-90 days decreasing to only 7% @ termination); **MRL:** CO_2 (max. 6% @ termination; **NER:** max. 9% @ termination	478320-13
Aerobic Soil Metabolism	Aberford Series (Site J1), UK sterilized then incubated @ 20 °C/ 40% of the **WHC**	**MAJ:** X-474 (max. 83% after 90 days then declined to 77% @ termination); **MIN:** None; **MRL:** CO_2 (max. <1% @ termination)**; NER:** max. 6% @ termination	478320-13
Aerobic/ Anaerobic Soil	Clay Loam Soil, TX**: Aerobic/Anaerobic Phases**	**MAJ:** X117194-74 (max. 95% after 20 days then declined to 75% @ termination); **MIN:** None; **MRL:** CO_2 (max. 0.45% @ termination); **NER:** max. 25% @ termination	478322-79

Property	*Soil or Water/Sediment System*	*Parent Degradation Products (% of Applied)*	*Reference (MRID)*
Metabolism	Aberford Series (Site J1), UK: **Aerobic/Anaerobic Phases**	**MAJ:** X117194-74 (max. 97 to 98% after 4 to 7 days then declined to 84% @ termination**); MIN:** None; **MRL:** CO_2 (max. 0.1% @ termination**); NER:** max. 12% @ termination	478320-13
Aerobic Aquatic Metabolism	**System 1:** Pond water/ sediment system , UK **System 2:** Pond water/ sediment system , UK	**MAJ:** X117194-74(max. ranging from 25 to 71% in system-1 and 47 to 66% in system-2 occurring at 61-103 days with no apparent decline); **MRL:** CO_2: max. 0.6 to1.5%, in systems 1 and 2, respectively, at study termination; **MIN:** max. 6 to 26% in systems 1 and 2, respectively @ termination	478320-14
Anaerobic Aquatic Metabolism	**System 3:** Pond water/ sediment system, VA **System 4:** Pond water/ sediment system, IA	**MAJ:** None; **MIN:** X-474 (max. 3% @ 14days in systems-3 and max. 8% @ study termination in system-4 (other replicate was only 3%); **MRL:** CO_2: <1% in systems-3 and 4 @ termination; **NER:** max.12 to 37% in systems-3 and 4, respectively @ termination	473723-11

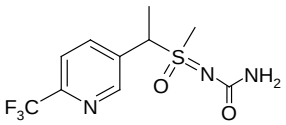
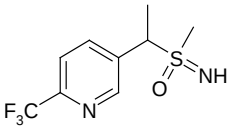
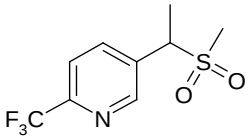
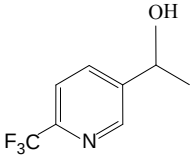
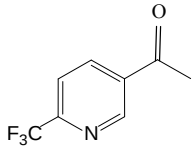


* Half-lives were >1,000 days in US soils with no degradates observed. In contrast, half-lives ranged from 85-381 days in EU soils producing degradate X-540 & X-457. Separate aerobic soil experiments showed that both of these degradates are persistent (90th percentile half-lives were 526 days (range 96 to 670 days) for X-457 and 2,808 days (range 71 to 3,630 days) for X-540

Figure 7. Expected environmental degradation pathways and transformation profiles for Sulfoxaflor

More details on laboratory biotic metabolism studies are included in **Appendix A**. Additionally, **Table 9** contains information about degradates of sulfoxaflor identified in varied biotic and biotic systems.

Table 9. Selected environmental degradates of sulfoxaflor

Characteristics	*Transformation Product*	*Structure*
Common Name	**X11719474 (X-474)**	
IUPAC	N-(methyl(oxido){1-[6-(trifluoromethyl) pyridin-3-yl]ethyl}-λ4-sulfanylidene) urea	
SMILES Code	c1c(ncc(c1)C(C)S(=NC(=O)N)(C)=O)C(F)(F)F	
Molecular Weight	297 g mole^{-1}	
Molecular Formula	$C_{10}H_{12}F_3N_3O_2S$	
Common Name	**X11579457 (X-457)**	
IUPAC	[5-[1-(S-methylsulfonimidoyl)ethyl]-2-(trifluoromethyl)pyridine	
SMILES Code	c1c(ncc(c1)C(C)S(=N)(C)=O)C(F)(F)F	
Molecular Weight	252.25 g/mole	
Molecular Formula	$C_9H_{14}F_3N_2OS$	
Common Name	**X11519540 (X-540)**	
IUPAC	5-(1-methanesulfonyl-ethyl)-2-trifluoromethyl-pyridine	
SMILES Code	c1c(ncc(c1)C(C)S(=O)(=O)C)C(F)(F)F	
Molecular Weight	253.24 g/mole	
Molecular Formula	$C_9H_{10}F_3NSO_2$	
Common Name	**X11721061 (X-061)**	
IUPAC	(1-[6-(trifluoromethyl)(2-14C)pyridin-3-yl]ethanol)	
SMILES Code	C1=CC(=NC=C1C(C)O)C(F)(F)F	
Molecular Weight	191.15	
Molecular Formula	$C_8H_8F_3NO$	
Common Name	**X11718922**	
IUPAC	1-(6-trifluoromethyl-pyridine-3-yl) ethanone	
SMILES Code	C1=CC(=NC=C1C(C)=O)C(F)(F)F	
Molecular Weight	189.14	
Molecular Formula	$C_8H_6F_3NO$	

c) Field Dissipation in Terrestrial Systems

Extensive data were collected from the terrestrial field dissipation (TFD) studies for sulfoxaflor (MRID 47832282). Complete analysis of the data is included in **Appendix A** and hereunder is a summary of these data. The terrestrial field dissipation (TFD) study for sulfoxaflor was designed based on the results of laboratory studies. These studies showed that sulfoxaflor degraded rapidly in soil, forming a major degradation product (X-474), and two minor degradation products (X-540 and X-457). Adsorption/desorption studies indicated that both parent sulfoxaflor and major/minor degradate (X-474, X-540 and X-457) are expected to be mobile. Additionally, sulfoxaflor and it degradate X-474 are systemic and were found to be stable to hydrolysis at pH 5, 7, or 9. Therefore, the TFD study design included leaching and plant uptake modules. Due to the low vapor pressure and Henry's law constant of sulfoxaflor, volatility in the field was not measured.

Five sites were selected for conducting bare and cropped-plots in California (CA), Florida (FL), North Dakota (ND), Ontario, Canada (ON), and Texas (TX). Sulfoxaflor soluble concentrate formulation (242 g active ingredient per litre of product or 22% w/w) was surface applied one to three times at nominal single rates ranging from 100g a.i./ha (equivalent to 0.089 lb a.i/A) to 200 g a.i./ha. The study design consisted of two treated plots (one cropped and one bare soil) and an untreated control plot at each study location (located at least 30 m from the treated plot). Treated and rotational crops representative of the geographical location of each test site were planted on areas designated for cropped plots over the course of the study. The California and Florida test sites were equipped with soil-suction lysimeters for the collection of soil-pore water samples. As required, supplemental irrigation (method not reported) was supplied to maintain at least 110% of long term average rainfall. The monthly target moisture input was set at 400% of the local historical average monthly precipitation in California and 120% in other sites. Other normal agronomic practices were followed.

Soil core samples were collected, for all sites, immediately after the first application to a depth of 6". Additionally, soil samples were collected from the soil profile to a depth of 36" at various sampling dates up to and including the end of the study (18 months in California, 15 months at other sites). The soil samples were extracted with 90:10 acetonitrile: 1.0 N hydrochloric acid (v: v) on a flat-bed shaker and extracts were concentrated prior to analysis. Soil pore-water samples were collected at depths of 3, 6, and 8 ft. in FL or 9 ft. in California at 1, 6, 13, 28 days and 2, 4, 6, 9, 12 and 15 months after the first treatment. Water samples were analyzed directly. Soil and water samples were analyzed for sulfoxaflor and its aerobic soil metabolite (X-474, X-540 and X-457) using HPLC) with positive-ion electrospray (ESI) tandem mass spectrometry (HPLC/MS/MS).

For at least one sampling event at each site, a set of transit stability samples were prepared to evaluate the stability of sulfoxaflor and its transformation products during shipment and storage. Soil samples were spiked at 1x and 100x the limit of quantification (LOQ= 0.001 ppm). Pore water samples were spiked at 1x and 40x the LOQ (0.05 ng/mL). Spiked samples were subjected to the same procedures as the field samples. Average recovery in transit stability soil samples ranged between 82 and 97% for sulfoxaflor, 94 and 125% for X-474, 77 and 101% for X-457, and 81.0 and 111% for X-540. Recovery in transit stability pore water samples was 88 % for

Sulfoxaflor, 95 and 88% for X-474, 85 and 84% for X-540, and 99 and 93% for X-457, in California and Florida, respectively.

Crop samples were collected at various crop growth stages during the first and second growing seasons and analyzed for sulfoxaflor, X474 (*i.e.*, the major soil metabolite)and X061 (*i.e.*, the plant metabolite) using a reverse-phase polymeric solid-phase extraction (SPE) cartridge on-line system using HPLC/MS/MS. The Method of Analysis limits of Detection/Quantification LOD/ LOQ and Performance were reported and were within acceptable limits. In addition application was verified by tank mix data, Soil deposition trays/saturated pads and zero-time concentrations.

A summary of the TFD Half-lives for parent Sulfoxaflor is included in **Table 10**.

Table 10. Field dissipation half-lives (DT50 in days) for sulfoxaflor from the top 6" of the soil and the entire soil profile (0-36")

		CALIFORNIA*		***FLORIDA****		***NORTH DAKOTA****		***ONTARIO****		***TEXAS****	
Chemical	***Considered Depth***	***Bare***	***Cropd***	***Bare***	***Cropd***	***Bare***	***Cropd***	***Bare***	***Cropd***	***Bare***	***Cropd***
Sulfoxaflor Parent	0-6" (top soil)	**2.0**	**1.9**	**0.7**	**1.6**	**0.3**	**0.1**	**0.6**	**0.9**	**8.1**	**1.5**
	0-36" (entire profile)	**ND**	**ND**	**ND**	**ND**	**ND**	**0.2**	**0.6**	**ND**	**8.1**	**1.5**

Bare= Bare soil plots; ***cropd***= cropped plots; **ND**= Not determined due to lack of data

Field leaching was also tested using soil pore water suction lysimeters to collect soil-pore water samples in two of terrestrial field dissipation studies: CA and FL. soil-suction lysimeters were installed at sampling depths of 3, 6, and 8 (FL) or 9 (CA) feet below ground surface. Soil-pore water samples were collected at -1, 6, 13, 28 days and 2, 4, 6, 9, 12 and 15 months after the first treatment. Although sulfoxaflor was not detected in pore water at any time/depth sampled in the high leaching profile in CA, it was concluded that non-detection was related to time of sampling rather than absence of leaching (*i.e.,* samples missed the leaching events).

Consistent with laboratory studies, major degradate X-474 was the major transformation product in the field dissipation studies. Data for the top 6" of the soil indicate the rapid formation of X-474 as its concentration of 13-54% of the applied parent was observed immediately following the first application. This was the case also following the second and third applications in CA and FL sites. Furthermore, data suggest that X-474 has the potential to carryover especially if leaching is limited (concentrations ranging from 1 to 18% of the applied parent were left in the soil after a year). Dissipation half-lives (DT_{50}) for X474 were calculated for residues in the top 6" of the soil and the whole 0-36" soil profile following the same procedure described for above for parent. Results are summarized in **Table 11**.

Table 11. Field dissipation half-lives (DT50) for major degradate X-474 from the top 6" of the soil and the entire soil profile (0-36")

Chemical	*Considered Depth*	*CALIFORNIA**		*FLORIDA**		*NORTH DAKOTA**		*ONTARIO**		*TEXAS**	
		Bare	*Cropd*	*Bare*	*Cropd*	*Bare*	*Cropd*	*Bare*	*Cropd*	*Bare*	*Cropd*
X-474 Degradate	0-6" (top soil)	**27**	**52**	**49**	**62**	**217**	**40**	**248**	**109**	**51**	**58**
	0-36" (entire profile)	**6**	**10**	**49**	**60**	**200**	**36**	**114**	**59**	**45**	**52**

Bare= Bare soil plots; ***cropd***= cropped plots; **ND**= Not determined due to lack of data

Data summarized in **Table 11** indicate that X-474 is much more persistent than its parent. Dissipation half-lives ranged from 49 to 248 days and from40 to 109 days in bare soil and cropped plots, respectively. Additionally, X-474 leached below the top 6" soil layers at all terrestrial field dissipation sites reaching 36, 30, 24, and 18" below the surface. At CA and FL sites, residues of X474 reached a depth of 36" with maximum concentrations of 19.5 to 20.6 ppb (≈19-20% of the applied parent) at 28 days after the 1st application in CA and maximum concentrations of 1.7 to 2.5 ppb (≈2-4% of the applied parent) at 2-15 months after the 1st application in FL. In ND, X-474 reached a depth of 30" with maximum concentrations of 1.0 to 2.3 ppb (≈2-4% of the applied parent) at 2-11 months after the 1st application. At ON (Canada) site, it reached a depth of 18" with maximum concentrations of 0.5-1.6 ppb (≈0.6-10% of the applied parent) at 9 months after the 1st application. At TX site, it reached a depth of 12" below the soil surface with maximum concentrations of 14.7 to 17.5 ppb (≈18-22% of the applied parent) at 4-9 months after the 1st application. Observed data confirm that field dissipation of X-474, from the top soil, is mainly related to transport (K_{oc}= 7 to 74 mL/g) rather than degradation.

Other Degradates: X-540 and X-457 were minor transformation products in the field. In most field sites, the two degradates dissipated from the 0-6 inch soil layer before the end of the study. The observed formation of minor quantities of degradates X-457 and X-540 is probably related to the relative high persistence of its most probable parent (the major degradate X-474). A kinetic analysis was not performed for X-540 and X-457.

Crop residue results for all five test sites were monitored for parent sulfoxaflor and its major transformation product X-474, as well as X-061 (a plant metabolite). Field plant data can be used to characterize foliage interception/uptake of applied parent and nature/concentration of residues in target and rotational crops. Other data were collected on nature and concentration of residues in target and rotational crops and summary/analysis of this data are included in **Appendix A**.

Top soil carryover is not expected for sulfoxaflor parent but is expected for X-474, X-457 and X-540. Estimated carryover for all of the three degradates were minimal (0-<1%) for CA site while it was significantly higher for FL, ND, ON and TX sites. For X-474, the maximum top soil carryover is estimated to be 15% for FL, 39% for ND, 40% for ON and 46% for TX. This is a reflection of the high formation/persistence of the degradate X-474. For X-540, the maximum top soil carryover is estimated to be 1% for FL, 4% for ND, 3% for ON and 5% for TX. For X-457, the maximum top soil carryover is estimated to be <2% in FL, ND, ON and TX.

d) Mobility

Laboratory adsorption data for sulfoxaflor indicate that the chemical can be characterized by very high to high mobility based on Freundlich organic carbon-based adsorption (K_{foc} ranged from 11-72 mL g^{-1} with an average of 35 mL g^{-1} and a median value of 31 mL g^{-1}). However, rapid degradation in soil is expected to limit the amounts of the chemical that may potentially leach and contaminate ground water. Contamination of groundwater by sulfoxaflor will only be expected when excessive rain occurs within a short period (few days) of multiple applications in vulnerable sandy soils.

Adsorption/desorption properties of parent sulfoxaflor and three of sulfoxaflor degradates were examined in seventeen soils for parent and X-474, seven soils for X-457 and six soils for X-540. Results for the adsorption phase are summarized in **Table 12** along with soils characteristics and locations.

Table 12. Transport properties Sulfoxaflor and its degradates

Soil: Geographic Location	*K_{foc} For Parent & Degradates L/Kg* [1]				*T; S; Si & C= Texture; Sand; Silt & Clay* [2]				*pH*	*% OC*	*CEC*
	Parent	*X-74*	*X-57*	*X-40*	*T*	*S%*	*Si%*	*C%*			
Lenawee: MI, USA	31	24	44	20	CL	31	35	34	5.9	1.8	16.9
Pullman-1: TX, USA	47	40	23	24	CL	31	34	35	6.9	1.2	23.2
Fayette: Iowa, USA	50	50	26	25	L	34	47	19	6.3	1.1	14.3
Slagle: VA, USA	34	21	35	ND	SL	54	30	16	6.4	1.0	5.0
M773: CA, USA	55	76	ND	ND	S	86	13	1	6.3	0.3	3.2
M774: FL, USA	53	31	ND	ND	LS	86	8	6	6.2	0.8	4.3
Bearden-Lindaas: ND, USA	72	68	ND	ND	C	17	32	51	7.9	1.8	36.0
Pullman-2: TX, USA	46	45	ND	ND	CL	27	38	35	6.7	1.1	21.5
Lacustrine: ON, Canada	29	23	ND	ND	L	31	46	23	6.9	1.8	8.9
Cranwell, Site I: Lincolnshire, UK	21	13	11	1	LS	81	16	3	7.6	1.3	9.2
Aberford, Site J1: Rutland, UK	12	7	2	6	L	49	32	19	7.3	6.7	37.9
Malham, Site E: Derbyshire, UK	11	8	10	6	SiL	28	59	13	6.2	3.5	20.3
LUFA 5M: Kreis Rheim-Pfalz, Germany	24	19	ND	ND	SL	61	26	13	7.4	1.2	6.3
M775: Bologna, Italy	31	32	ND	ND	SCL	54	23	23	7.4	1.3	13.2
M776: Valencia, Spain	30	22	ND	ND	CL	42	30	28	7.8	1.2	9.8
M780: Haine-Et-Loire, France	20	14	ND	ND	CL	43	24	33	7.8	1.7	15.6
M781: Lower Saxony, Germany	23	18	ND	ND	SL	19	62	19	6.3	1.1	10.0
Average Values	**35**	**30**	**22**	**14**							
Median Values	**31**	**23**	**23**	**13**							

[1] Degradates: ***X-74***= X11719474; ***X-57***= X11579457; ***X-40***= X11519540; ND= Not determined

[2]CL= Clay Loam; L= Loam; SL= Sandy Loam; S= Sand; LS= Loamy Sand; C= Clay; SiL= Silt Loam; SCL= Sandy Clay loam

Data for Freundlich organic carbon based adsorption (K_{foc}; **Table 12**) indicates that parent sulfoxaflor and it degradates are expected to be highly mobile to mobile in soil systems (FAO,

2000)[5]. One desorption cycle was carried out for parent sulfoxaflor and transformation products were not subjected to the desorption step. Freundlich desorption isotherms (K_f) ranged from 0.18 to 0.89 (K_{foc} of 9-61 suggesting that parent sulfoxaflor will not bind irreversibly and that some material will desorb from the soil.

e) Environmental Chemistry Methods and Independent Laboratory Validation

Table 13 contains a summary of the analytical methods to be used for determining concentrations of parent sulfoxaflor and degradates in soil, water, and air. The limit of quantification established for each method/analyte is also included in the same Table.

Table 13. Summary of analytical methods (residue) for soil, water and air (method type for all analytes= LC/MS/MS)

Method ID	*LOQ (For All Analytes)*	*Reference MRID*
Soil (Analytes: Sulfoxaflor, X11519540 (X-540), X11579457 (X-457) and X11719474 (X-474)		
(1) Dow AgroSciences Study Number 091185	0.001 mg/kg	47832269
(2) Dow AgroSciences Study Number 101100	0.001 mg/kg	47832256
(3) Pyxant Labs Inc. Study Number 081078-1906A	0.001 mg/kg	47832270
Water (Analytes: Sulfoxaflor, X11519540 (X-540), X11579457 (X-457) and X11719474 (X-474)		
(1) Dow AgroSciences Study Number 091186	0.05 µg/L (with SPE); 0.25 µg/L (without SPE)	47832268
(2) Dow AgroSciences Study Number 101650	0.05 µg/L (with SPE)	47832267
(3) Pyxant Labs Inc. Study Number 081078-1906B	0.05 µg/mL	47832266
Air		
Not reviewed; not required for registration in the United States; Not expected to partition into the air.		47832265

The soil method is applicable for the quantitative determination of residues of Sulfoxaflor and its metabolites (X-540, X-457, and X-474) in soil (MRID 47832269). Validation was conducted using four soil types; the soil textural classifications were silt loam, sandy loam, clay loam, and loam. The method was validated over a concentration range of 0.001-1.0 mg/kg with a validated limit of quantitation of 0.001 mg/kg and limit of detection of 0.0003 mg/kg (MRIDs 37832256 and 47832270). The mean recovery for fortified control samples was within the acceptance

[5] Food and Agriculture Organization of the United Nations (FAO), 2000. FAO pesticide disposalseries 8. Assessing soil contamination: A reference Manual. Appendix 2. Parameters of pesticides that influence processes in the soil. Editorial Group, FAO Information Division, Rome.

range of 70-110% with a relative standard deviation (RSD) of ≤20% with one exception. The average recovery for X-540 at the 0.010-mg/kg level was 113%; however, the data was considered valid as RSD was less than 6% for 29 replicates.
The water method is applicable for the quantitative determination of residues of sulfoxaflor and its metabolites (X-457, X-540, and X-474) in drinking water (tap water), ground water (well water), and surface water (pond water) (MRID 47832268). The method was executed with and without a solution purification step using an online reverse-phase polymeric solid-phase extraction (SPE) cartridge. The method was validated over a concentration range of 0.050-50.0 µg/L (MRID 47832267) with a validated limit of quantitation was:

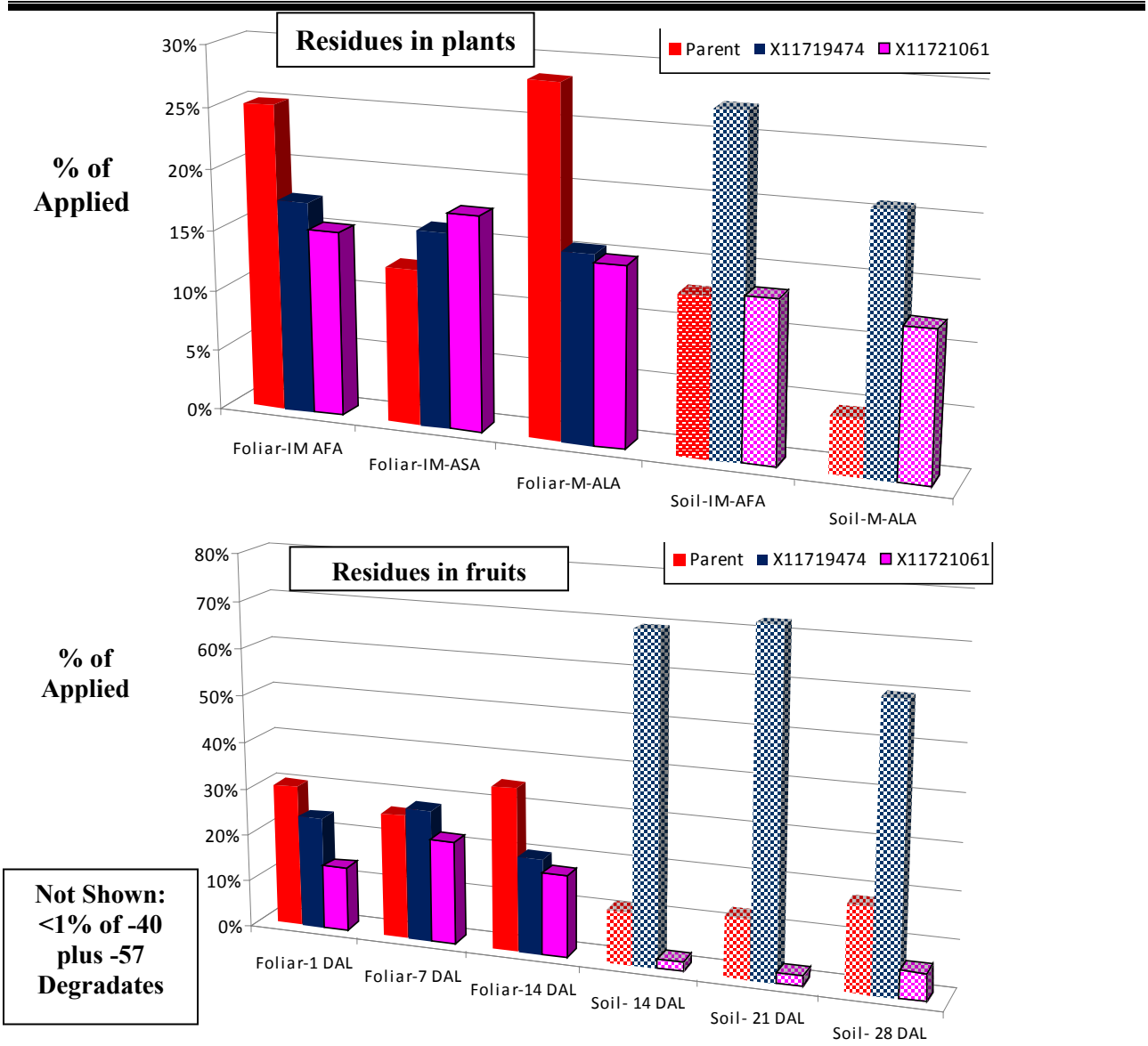
- 0.050 µg/L when the SPE step is included; and
- 0.250 µg/L when the SPE is not included

The mean recovery for fortified control samples was within the acceptance range of 70-110% with a relative standard deviation (RSD) of ≤20%.
For ground water (pore water), the method is applicable for the quantitative determination of residues of sulfoxaflor, and its major metabolites (X-457, X-540, and X-474) in ground water (soil pore). The method was validated over a concentration range of 0.050-2.00 µg/L with a validated limit of quantitation of 0.050 µg/L (MRID 47832266).

f) Metabolism, Distribution and Expression of Residues in Plants

Sulfoxaflor is a systemic pesticide; therefore it is important to analyze available plant data toward understanding how exposure pathways may be affected by plants. A study was conducted, on tomato plants, where ^{14}C sulfoxaflor was foliarly applied in one experiment and was soil applied in another[6]. In the foliar application experiment, the chemical was applied four times/directly into foliage at a seasonal total of 600 g a.i/ha. In the soil application experiment, ^{14}C-sulfoxaflor was applied twice/directly into the soil at a seasonal total rate of 400 g a.i/ha. A summary of the data for both experiments are included in **Figure 8**.

[6] Rotondaro, S. L., Balcer, J. L., and Smith, K. P. A Nature of the Residue Study with 14C-SULFOXAFLOR Applied to Tomatoes, Unpublished report of Dow AgroSciences, study ID 070021, 22 February 2010, amended 24 March 2010.



Foliar/Soil= foliar "solid columns"/soil application "hatched columns"; **IM/M**= immature/mature plants**;**
AFA/ASA/ALA= after 1st/2nd/Last Application; **DAL**= days after last application
Chemical source: Foliar= from Foliar applied parent; Soil= from Soil applied parent

Figure 8. Distribution of sulfoxaflor residues in tomato following foliar and soil applications

As shown in **Figure 8**, the majority of the radioactive residue in the foliar-applied tomato plants was identified as parent followed by two degradates: X117194-74 and X117210-61. Plant metabolism appears to produce the two degradates in parallel from parent and in sequence from parent to X-474 to X-061. It is noted that reported aerobic soil metabolism data (elsewhere in this document) show that degradate X-474 is the major aerobic soil degradate of sulfoxaflor while X-061 is not a product of this route of degradation. In this foliar experiment, the only

source of sulfoxaflor is foliage as it was not applied to soil. Presence of sulfoxaflor and degradates X117194-74 and X117210-61 in the plant, suggest that parent sulfoxaflor entered the plant from foliage and was subjected to plant metabolism producing degradates X-474 and X-061. Therefore, both of these degradates can be considered as plant metabolism degradates.

In contrast to foliage, the majority of the radioactive residues in the tomatoes proper were identified as the degradate X-474 followed by substantially lower concentrations of parent and X-061 (**Figure 8**). The noticeable increase of X-474 in tomato foliage suggests the presence of an additional source for X-474 (*e.g.*, root uptake from soil). It appears that sulfoxaflor parent was subjected to three parallel processes: movement into plant as parent (source of parent in the plant), degradation in the soil producing X-474 that also appear to move into the plant via root uptake, plant metabolism (reducing parent concentration entering the plant with production of additional amounts of X-474 in addition to X-061). In the plant, the combined results of these three processes are high X-474 concentration (movement from soil plus production in plant) and low concentration of. These residue studies suggest that similar to the parent, X-474 is systemic and that it can be produced by soil and plant metabolism.

Equivalent metabolism studies were executed for succulent peas[7], three foliar applications, a total of 601 g a.i./ha; and two soil applications, totaling 434 g a.i./ha), lettuce (MRID ?[8], three foliar, one on immature plants and two on mature plants, totaling 599 g a.i./ha along with one soil application at a rate of 454 g a.i./ha) and rice[9], three foliar application, totaling 578 g a.i./ha along with one soil application at a rate of 474 g a.i./ha). Maximum observed concentrations for sulfoxaflor parent and degradates are summarized in **Figure 9** for all studies including tomatoes.

[7] Hastings, M. J., Rotondaro, S. L., and Balcer, J. L. A Nature of the Residue Study with [14C]-XR-208 Applied to Peas, Unpublished report of Dow AgroSciences, study ID 070035, 13 May 2010.
[8] Graper, L. K., Balcer, J. L., and Smith, K. P. A Nature of the Residue Study with [14C]-XDE-208 Applied to Lettuce, Unpublished report of Dow AgroSciences, study ID 070033, 01 June 2010.
[9] Rotondaro, S. L., Balcer, J. L., and Smith, K. P. A Nature of the Residue Study with 14C-XDE-208 Applied to Rice, Unpublished report of Dow AgroSciences, study ID 070034, 23 December 2009, amended 13 January 2010 and 24 March 2010.

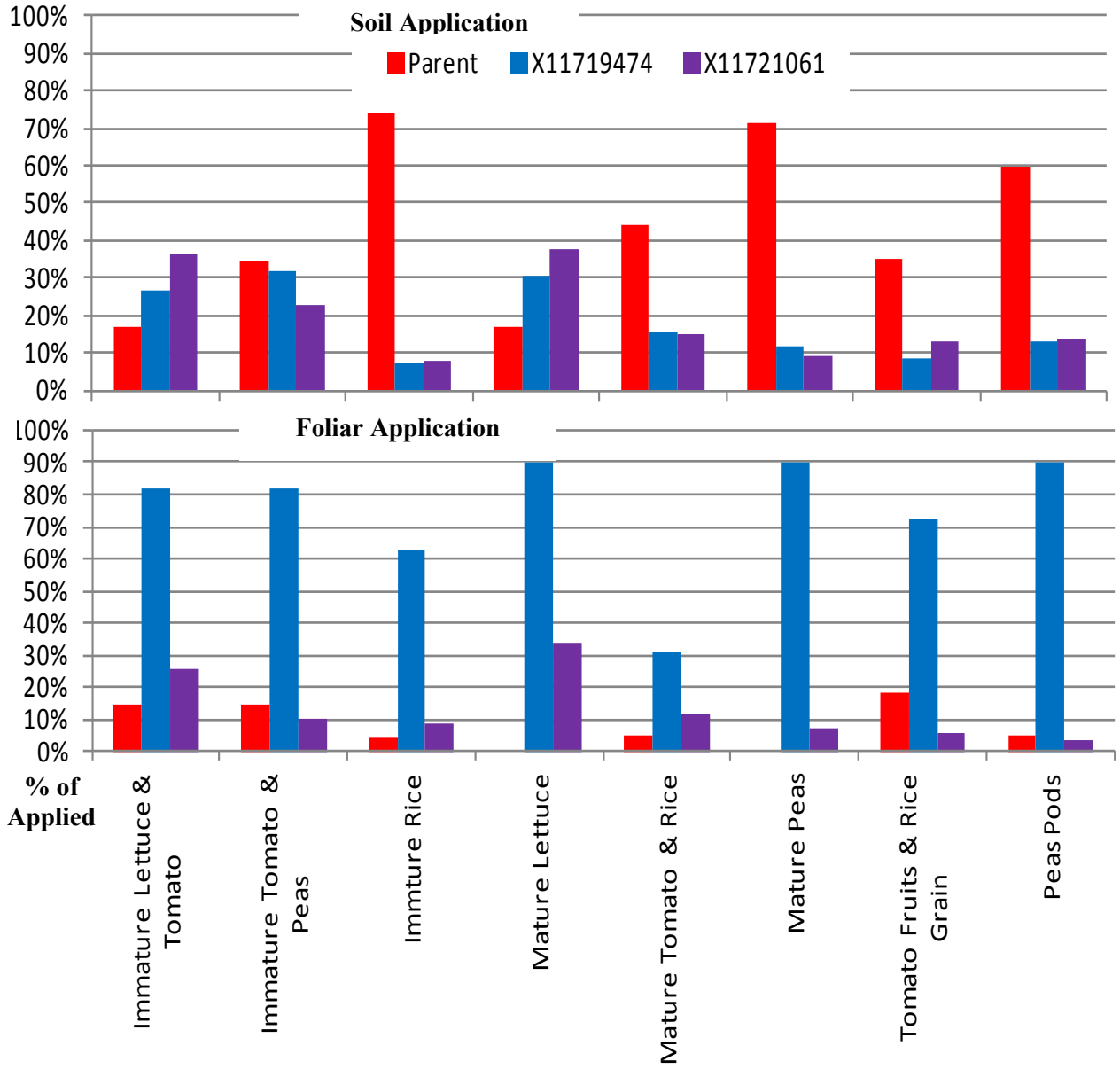


Figure 9. Distribution of maximums of sulfoxaflor residues in four crops following foliar and soil applications

Data depicted in **Figure 9** indicate that when sulfoxaflor is applied to foliage it enters immature plants giving varied maximum concentrations (rice> tomatoes& peas> lettuce). In contrast, only limited sulfoxaflor parent enters the plant before it degrades into X-474 which appears to be what enters the plants giving relatively high concentrations (over 60% with tomato, lettuce & peas> rice). The level of "soil originated parent sulfoxaflor" that enters the plant is relatively low due to the fact that parent is not expected to be available in the soil system due to its rapid degradation. As plants mature, tissues appear to retain "foliage originated parent sulfoxaflor" at

the same level in peas, lower level in rice and at higher level in tomato. In fruits, grain and pods, the level of "foliar originated parent sulfoxaflor" is maintained with concentration ranging from 30 to 60%. "Soil originated X-474" appear to show similar patterns to its parent with relatively higher concentrations. Plant metabolism of foliage or soil originated parent and degradate X-474 appears to be occurring at all stages of plant development producing X-061 and other degradates. The pattern of formation and decline for parent and degradate is difficult to deduce due to the apparent occurrence of multiple processes including degradation and translocation; within the plant and from soil/foliage to plant.

When sulfoxaflor is applied foliarly on growing crops it is intercepted by the crop canopy. Data presented above appear to indicate that sulfoxaflor enters the plant and is incorporated in the plant foliage with only limited degradation. It appears that this is the main source of the insecticide sulfoxaflor that would kill sap sucking insects. This is because washed-off sulfoxaflor, that reaches the soil system, is expected to degrade rapidly to the main degradate X-474 (aerobic soil $90^{\%tile}$ $t_{½}$= 0.4 day). Additionally, plant data suggest that the degradate X-474 is systemic as well and is expected to enter the plant from the soil. No data were presented on the insecticidal activity of this degradate.

g) Expected Behaviour of Sulfoxaflor in an Agricultural Setting

Sulfoxaflor is proposed for application to variable density foliage of growing crops that depends on the timing of application (in all crops, the application window spans from seedlings to harvest). Upon application, only limited quantities of the pesticide are expected to be carried away by drift (to adjacent terrestrial and aquatic systems) with the majority being deposited on target plants. Additionally, part of the applied pesticide is deposited into the soil with amounts being dependent on treated crop foliage density and wash-off from foliar surfaces.

Sulfoxaflor deposited on the plant foliage is available for plant uptake. Plant residue data indicate that the parent compound enters the plant and is distributed into the foliage with only limited degradation (depending on the plant). The same data also suggest that the degradate X-474 is systemic and can enter the plant from the soil (following its formation from rapid parent degradation). Parent entering the plant through foliage and X-474 entering the plant from soil may be a source of exposure depending on the agricultural practices. In contrast, sulfoxaflor, reaching the soil system directly and/or from foliage wash-off, will be subjected to rapid degradation to X-474 (main soil degradate) which further degrades in most soils very slowly producing relatively low concentrations of X-540 and X-457.

h) Fish Bioconcentration

No Fish bioconcentration study was submitted due to the low K_{ow} (K_{ow} @ 20 C & pH 7= 6; Log K_{ow} = 0.802). Based on the low K_{ow}, sulfoxaflor is not expected to bioaccumulate in aquatic systems. Although the parent compound has a high K_{OA} which signifies a potential for bioaccumulation in terrestrial ecosystems, sulfoxaflor is not expected to move into the air in appreciable concentrations based on its physical-chemical properties.

3.2.2. Measures of Aquatic Exposure

Aquatic exposures are quantitatively estimated for all of assessed uses using scenarios that represent high exposure sites for sulfoxaflor use. Each of these sites represents a 10-hectare field that drains into a 1-hectare pond that is 2 meters deep and has no outlet. Exposure estimates generated using the standard pond are intended to represent a wide variety of vulnerable water bodies that occur at the top of watersheds including prairie pot holes, playa lakes, wetlands, vernal pools, man-made and natural ponds, and intermittent and first-order streams. As a group, there are factors that make these water bodies more or less vulnerable than the standard surrogate pond. Static water bodies that have larger ratios of drainage area to water body volume would be expected to have higher peak EECs than the standard pond scenario. These water bodies will be either shallower or have large drainage areas (or both). Shallow water bodies tend to have limited additional storage capacity, and thus, tend to overflow and carry pesticide in the discharge whereas the standard pond has no discharge. As watershed size increases beyond 10 hectares, at some point, it becomes unlikely that the entire watershed is planted to a single crop, which is all treated with the pesticide. Headwater streams can also have peak concentrations higher than the standard pond, but these higher concentrations tend to persist for only short periods of time and are then carried downstream.

The objectives of this approach are to determine the EECs for the total toxic residues (TTR) of parent sulfoxaflor which represent the stressor of concern in aquatic systems. Based on the toxicity of parent sulfoxaflor and important degradates, *i.e.*, X-474 and X-540 to aquatic organisms, only parent and X-540 are considered in estimating the EECs of the stressor.

However exposure is dominated by the degradate X-474 and in order to understand the exposure of parent and its degradation products, EECs for parent and each of the individual constituents of the parent residues, namely, parent, X-474, and X-540 were also estimated by running the following simulations:

a. Residues of interest runs for scenarios representing all crop use patterns with ground and aerial application (a total of 50 runs using EXPRESS graphical interface);
b. Residues of interest runs for scenarios representing all crop use patterns with aerial application; varied first application dates "5-15 runs through the long application window for this chemical" (using PE-5 graphical interface);
c. Residues of interest runs for the same scenarios including two runs: one with drift and the other without drift (using PE-5 graphical interface); and
d. Parent alone runs for the same scenarios (using PE-5 graphical interface).

Hereunder, is a complete list of the steps taken to perform modeling:

(1) ***Model Runs Residues of Interest and Parent (all Crops Except Watercress)***

a. Inputs Used for Modeling

The first set of input parameters needed for modeling is labeled application parameters for various use patterns. Currently suggested labeled application parameters for sulfoxaflor are summarized in **Table 14**.

Table 14. Crop use patterns proposed for sulfoxaflor (Ground or aerial is permitted for all uses (refer to exceptions stated below this Table for Turf and ornamentals)

Crop/Crop Group	*Crop Group(CG) Or Subgroup (SG)*	*Application Parameters: Maximum Application Rates/ Number& Minimum Intervals (Days) & Window*				
		*Single (lb a.i./A)**	*Number*	*Yearly (lb a.i./A)**	*Intervals*	*Window***
Beans	Beans	0.090	3			**For crops:** from date of seedling to pre-harvest taking into consideration the pre-harvest interval (PHI) for each crop PHI ranges from 1 to 14 days) **For trees:** from Pre-bloom to mature fruit
Berries	SG 13-07F &G	0.090	3	0.266	7	
Canola (Rapeseed)	SG 20A	0.043	2	0.090	14	
Citrus	CG 10	0.133	2		7	
Cotton	Cotton	0.090	3		5	
Fruits: Pome	CG 11	0.133	2		7	
Fruits: Stone	CG 12	0.133	2	0.266	7	
Grains (small grains)	Small Grains	0.043	2	0.090	14	
Ornamentals	Ornamentals	0.133	2			
Soybeans	Soybeans	0.090	3			
Tree Nuts	CG 14 & Pistachio	0.133	2			
Turf grass	Turf grass	0.133	2			
Vegetables: Brassica (cole) leafy	CG 5	0.090	3			
Vegetables: Bulb	SG 3-07	0.090	3			
Vegetables: Cucurbit	CG 9	0.090	3			
Vegetables: Fruiting & Okra	CG 8 & Okra	0.090	3			
Vegetables: Leafy except Brassica	CG 4	0.090	3			
Vegetables: Root & tuber /Leaves	CG 1 & 2	0.090	3			
Watercress (commercial production)	Watercress	0.090	3	0.266	7	

Exceptions: (1) Only to commercial sod farms and grass grown for seed applied only by ground; and
(2) May be applied aerially only to commercially grown ornamentals

* Application rates entered into PRZM/EXAMS modeling are in Kg/ha= lbs/A multiplied by 1.121. For example: the maximum single application rate for beans= 0.09 x 1.121= 0.101 kg/ha and the yearly rate= 0.266 x 1.121= 0.298 kg/ha

** * Expected application date: This date is the date giving the highest EEC among multiple dates within the labeled application windows: from pre-bloom to mature fruits for trees and from seeding to harvest for all others. Starting and ending dates for windows were taken from the scenarios. Multiple runs were executed for each scenario with dates of application The number of runs executed for each scenario. Actual application dates chosen for various scenarios are included in **Appendix A**.

The second set of input parameters needed for modeling involves choosing crop scenarios to represent the proposed use patterns. All available standard scenarios were used for modeling to

represent labeled crop use patterns. A list of these scenarios along with the required application parameters is presented in **Table 15**.

Table 15. List of scenarios and application parameters used in modeling

			Application Parameters (No.= Number of Applications)	
Crop/Crop Group	*Crop(s)*	*Scenario*	*Rate (lb a.i/A) X No.[1]*	*Intervals (Days)*
Beans	Beans (dry & Lima, snab)	MIbeansSTD	0.090 x 3	7
Beans	Beans (dry & Lima, snab)	ORsnbeansSTD	0.090 x 3	7
Berries	Berries & Strawberry	FLstrawberrySTD*	0.090 x 3	7
Canola (Rapeseed)	Rape seed	NDcanolaSTD	0.043 x 2	14
Canola	mustard greens	FLcabbageSTD	0.043 x 2	14
Canola	Sesame	CAcottonSTD*	0.043 x 2	14
Canola	Sesame	MScottonSTD	0.043 x 2	14
Canola	Sesame	MSsoybeanSTD	0.043 x 2	14
Canola	Sesame	NCcottonSTD	0.043 x 2	14
Citrus	Citrus	FLcitrusSTD	0.133 x 2	7
Citrus	Citrus	CAcitrusSTD*	0.133 x 2	7
Cotton	Cotton	NCcottonSTD	0.090 x 3	5
Cotton	Cotton	MScottonSTD	0.090 x 3	5
Cotton	Cotton	CAcottonSTD*	0.090 x 3	5
Fruits: Pome & Stone	Apples, Peaches & Cherries	CAfruitSTD*	0.133 x 2	7
Fruits: Pome	Apples, pears & Quince	NCappleSTD	0.133 x 2	7
Fruits: Pome	Apples, pears & Quince	ORappleSTD	0.133 x 2	7
Fruits: Pome	Apples, pears & Quince	PAappleSTD_V2	0.133 x 2	7
Fruits: Stone	Peaches &/Or Cherries	GAPeachesSTD	0.133 x 2	7
Fruits: Stone	Peaches &/Or Cherries	MICherriesSTD	0.133 x 2	7
Grains (small grains)	Barley, Triticale & Wheat	NDwheatSTD	0.043 x 2	14
Ornamentals	X-mass Trees	ORXmasTreeSTD	0.133 x 2	7
Ornamentals	Ornamentals	CAnurserySTD_V2	0.133 x 2	7
Ornamentals	Ornamentals	MInurserySTD_V2	0.133 x 2	7
Ornamentals	Ornamentals	NJnurserySTD_V2	0.133 x 2	7
Ornamentals	Ornamentals	FLnurserySTD_V2	0.133 x 2	7
Ornamentals	Ornamentals	TNnurserySTD_V2	0.133 x 2	7
Soybean	Soybean	MSsoybeanSTD	0.090 x 3	7
Tree Nuts	Almonds	CAalmondSTD*	0.133 x 2	7
Tree Nuts	Filberts	ORfilbertsSTD	0.133 x 2	7
Tree Nuts	Pecans	GAPecansSTD	0.133 x 2	7
Turf grass	Turf	FLturfSTD	0.133 x 2	7
Turf grass	Turf	PAturfSTD	0.133 x 2	7

Crop/Crop Group	Crop(s)	Scenario	Application Parameters (No.= Number of Applications)	
			Rate (lb a.i/A) X No.[1]	Intervals (Days)
Vegetables: Brassica (cole) Leafy	Several **	FLcabbageSTD	0.090 x 3	7
Vegetables: Bulb	Onion (dry/green) & Pearl	CAonionSTD*	0.090 x 3	7
Vegetables: Bulb	Onion (dry/green) & Pearl	GAOnionSTD*	0.090 x 3	7
Vegetables: Cucurbit	Cucumber, Melons	NJmelonSTD	0.090 x 3	7
Vegetables: Cucurbit	Cucumber, Melons	MOmelonSTD	0.090 x 3	7
Vegetables: Cucurbit	Cucumber, Melons	MImelonSTD	0.090 x 3	7
Vegetables: Cucurbit	Cucumber, Melons	FLcucumberSTD	0.090 x 3	7
Vegetables: Fruiting & Okra	Pepper	FLpeppersSTD	0.090 x 3	7
Vegetables: Fruiting & Okra	Tomato, Eggplant & Okra	PAtomatoSTD	0.090 x 3	7
Vegetables: Fruiting & Okra	Tomato, Eggplant & Okra	FLtomatoSTD	0.090 x 3	7
Vegetables: Fruiting & Okra	Tomato, Eggplant & Okra	CAtomatoSTD*	0.090 x 3	7
Vegetables: Leafy	Parsley	ORmintSTD	0.090 x 3	7
Vegetables: Leafy except Brassica	Lettuce/Celery/ Spinach	CAlettuceSTD	0.090 x 3	7
Vegetables: Root & tuber	Carrot & Burdock (edible)	FLcarrotSTD	0.090 x 3	7
Vegetables: Root & tuber	Potatoes, Turnip& Rutabaga	MEpotatoSTD	0.090 x 3	7
Vegetables: Root & tuber	Potatoes, Turnip& Rutabaga	IDNpotatoSTD*	0.090 x 3	7
Vegetables: Root & tuber	Sweet Potatoes	NCSweetPotatoSTD	0.090 x 3	7
Vegetables: Root & tuber	Beet & Ginseng	MNsugarbeetSTD	0.090 x 3	7

[1] Application rates entered into PRZM/EXAMS modeling are in Kg/ha= lbs/A multiplied by 1.121. For example: the maximum single application rate for beans= 0.09 x 1.121= 0.101 kg/ha and the yearly rate= 0.266 x 1.121= 0.298 kg/ha
* Scenarios with irrigation
** including: Broccoli, Brussels sprouts, Cabbage, Cauliflower, Kale

The third set of input parameters needed for modeling is the fate and transport characteristics of the chemicals being modeled. These parameters are summarized in **Table 16** for the residues of interest and ***parent*** runs.

Table 16. Summary of PRZM/EXAMS input parameters for modeling Sulfoxaflor parent and residues of interest

Input Parameter (Unit)	*Value for Residues of Interest* (Parent)*	*Reference (MRID No) and Notes*
Molecular Weight g/mole	277.27 (for both)	Product chemistry
Henry's constant (atm-m^3 mol^{-1} *@ 25 °C)*	1.2 x 10^{-11} (for both)	Calculated

Input Parameter (Unit)	*Value for Residues of Interest* (Parent)*	*Reference (MRID No) and Notes*
Solubility in Water(mg/L)	570 (for both)	Product chemistry
Photolysis in Water (t½ in days @ pH 7)	Stable (for both)	Because the only photolysis degradate is included **(MRID 478322-83)**
Aerobic Soil Metabolism (90th % t½ in days)	1,502 (0.4)	**(MRIDs 478655-78 and 478320-13)**
Hydrolysis (90th % t½ in days)	Stable (for both)	**(MRID 478321-49)** All degradates are considered stable
Aerobic Aquatic Metabolism (90th % Whole system t½ in days)	1,577 (141)	**(MRID 478320-14)**
Anaerobic Aquatic Metabolism (90th % Whole system t½ in days)	873 (672)	**(MRID 478322-77)**
K_{oc} (Average in L/Kg)	14 (35)	**(MRID 478320-14)** Use Koc for X-540
Chemical Application Method (CAM)	2	
Application Efficiency	95% for aerial 99% for ground	
Spray Drift Fraction	Aerial (0.05) Ground: Airblast (0.01) and others (0.03)	Parameter Guidance[10]

* Half-life values for the residues of interest are calculated from data for parent + X-474 + X-540. Note that half-life values reported earlier in the fate section are as specified either for parent or X-474 or X-540.

b. Model Residues of Interest for Ground & Aerial Applications Using EXPRESS

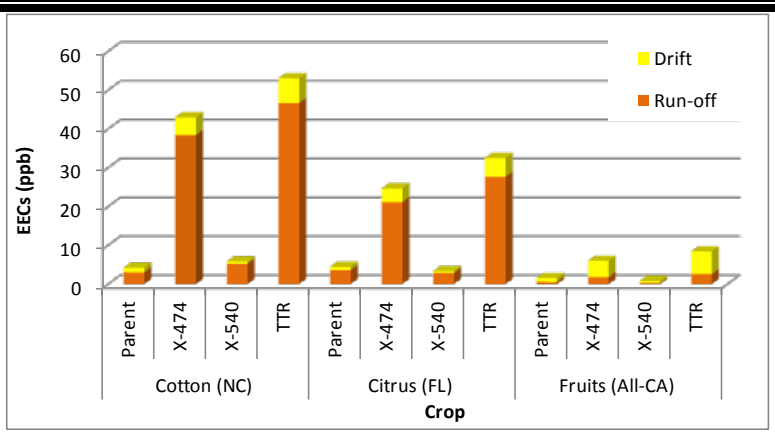
Model runs were executed to determine if ground application gives higher EECs than aerial application. As expected, aerial application gave higher EECs compared to ground application, therefore modeling concentrated on aerial application and the results for ground application are not included in this assessment.

The results for these multiple runs gave total, drift and run-off surface water associated EECs for parent (from parent runs), X-474 (estimated to be 88% of "Residues of interest minus parent"), X-540 (estimated to be 12% of "Residues of interest minus parent")[11], and EECs for the total of parent+ X-540+X-474. **Figure 10** shows an example graphical representation for some of these results.

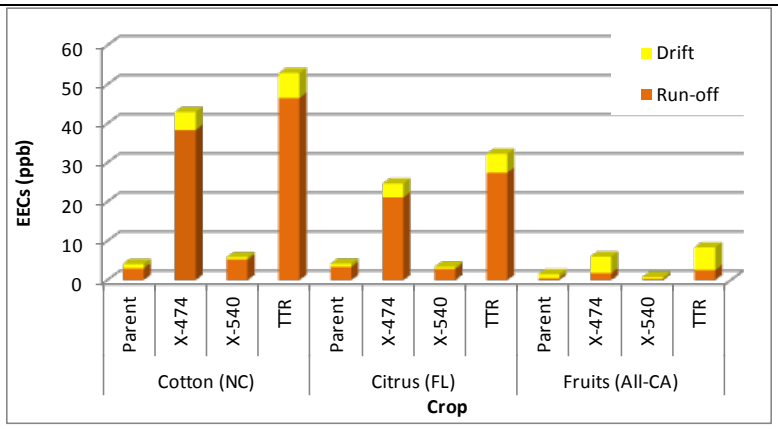
[10] Guidance for Selecting Input Parameters in Modeling the Environmental Fate and Transport of Pesticides. URL: http://www.epa.gov/oppefed1/models/water/input_parameter_guidance.htm

[11] Based on the maximum residues of 12% X-540 found in aerobic soil where it is expected to form.

Peak



21-day



60-day

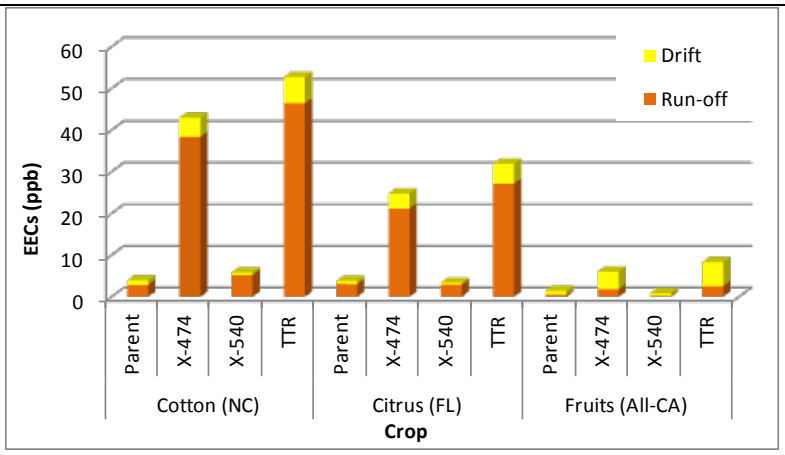


Figure 10. Surface water peak/21-day/60-day for the residues of interest EECs (µg/L) from cotton and others

RQs were calculated for the EECs of the residues of interest (total of parent+ X-540+X-474) and based on the results only scenarios predicting risk were used to arrive at EECs for the TTR (parent+ X-540). The latter were calculated from parent alone runs as follows:

(1) Parent EECs from parent runs;

(2) X-540 EECs from parent runs (12% of parent due to run-off + 0% of parent due to drift). This is based on the facts that the source of X-540 degradate is expected to be run-off from the soil only (X-540 did not form in laboratory aquatic systems) and that the maximum observed was 12%; and
(3) EECs for the TTR by adding EECs from (1) and (2) above.

EECs for the TTR from the selected scenarios are summarized in **Table 17** for surface water and in **Table 18** for pore water.

Table 17. Surface water EECs (µg/L) of the TTR for Sulfoxaflor use patterns

Crop (State)	*Crop Group(s)*	*Crop(s)*	*Scenario*	*DATE*	*Peak*	*21-day*	*60-day*
Beans (MI)	CG-6	Beans (dry & Lima, snab)	MIbeansSTD	29m07	5.5	5.31	5.05
Citrus (FL)	CG-10	Citrus	FLcitrusSTD	08m04	4.9	4.61	4.16
Cotton (NC)	Cotton	Cotton	NCcottonSTD	23m09	4.6	4.46	4.26
Cotton (MS)	Cotton	Cotton	MScottonSTD	26m08	4.6	4.35	4.02
Vegetables: Brassica (cole) Leafy	CG-5	Broccoli, Brussels sprouts, Cabbage, Cauliflower, Kale	FLcabbageSTD	06m05	1.1	1.01	0.91
Vegetables: Bulb (GA)	CG-3-07	Onion (dry/green) & Pearl	GAOnion_WirrigSTD	26m08	3.1	2.93	2.76
Vegetables: Leafy except Brassica	CG-4	Lettuce/Celery/ Spinach	CAlettuceSTD	22m04	1.7	1.62	1.55
Vegetables: Root & tuber	CG-1& 2	Potatoes, Turnip& Rutabaga	MEpotatoSTD	26m08	2.5	2.48	2.43
Vegetables: Root & tuber	CG-1& 2	Sweet Potatoes	NCsweetpotatoSTD	26m08	4.2	4.01	3.81

Table 18. Pore water EECs (µg/L) of the TTR for Sulfoxaflor use patterns

Crop (State)	*Crop Group(s)*	*Crop(s)*	*Scenario*	*DATE*	*Peak*	*21-day*	*60-day*
Beans (MI)	CG-6	Beans (dry & Lima, snab)	MIbeansSTD	29m07	4.06	4.06	4.04
Citrus (FL)	CG-10	Citrus	FLcitrusSTD	08m04	2.67	2.67	2.63
Cotton (NC)	Cotton	Cotton	NCcottonSTD	23m09	3.37	3.32	3.13
Cotton (MS)	Cotton	Cotton	MScottonSTD	26m08	3.40	3.35	3.26
Vegetables: Brassica (cole) Leafy	CG-5	Broccoli, Brussels sprouts, Cabbage, Cauliflower, Kale	FLcabbageSTD	06m05	0.65	0.65	0.64
Vegetables: Bulb (GA)	CG-3-07	Onion (dry/green) & Pearl	GAOnion_WirrigSTD	26m08	2.02	2.02	1.99

Vegetables: Leafy except Brassica	CG-4	Lettuce/Celery/ Spinach	CAlettuceSTD	22m04	1.33	1.33	1.33
Vegetables: Root & tuber	CG-1& 2	Potatoes, Turnip& Rutabaga	MEpotatoSTD	26m08	2.48	2.47	2.45
Vegetables: Root & tuber	CG-1& 2	Sweet Potatoes	NCsweetpotatoSTD	26m08	3.21	3.21	3.20

a) Estimation of Sediment Concentrations

Exposure EECs to benthic sediment in aquatic systems was obtained for the highest and lowest pore water EECs (**Table 19**).

Table 19. Sediment EECs (µg/kg) for scenarios giving the highest and lowest pore water EECs

Crop (State)	*Crop Group(s)*	*Crop(s)*	*Scenario*	*DATE*	*Peak*	*21-day*	*60-day*
Beans (MI)	CG-6	Beans (dry & Lima, snab)	MIbeansSTD	29m07	7.19	7.18	7.15
Vegetables: Brassica (cole) Leafy	CG-5	Broccoli, Brussels sprouts, Cabbage, Cauliflower, Kale	FLcabbageSTD	06m05	1.15	1.14	1.13

(2) Model Runs for Watercress)

a. Inputs Used for Modeling

Watercress is typically cultivated in shallow, flowing water 2-3 inches deep[12]. The Agency does not currently have a methodology for exposure assessment for crops cultivated in flowing water. In this assessment, conservative EECs resulting from application of sulfoxaflor to watercress were quantitatively obtained using Tier 1 Rice Model. It is noted however, that conservatism in the estimates comes from two assumptions:

(1) The assumption that the pesticide is applied to water although commercial production appear to indicate that the pesticide is to be applied only to the plant foliage with no water present; and
(2) The assumption that surface water EECs is equal to that expected by direct application of the pesticide into a rice paddy. Therefore, modeling results were characterized to reflect effects of application efficiency (fraction of amount applied which is intercepted by the crop), degradation of the pesticide in water after application, and effects of flow through and downstream from the area of cultivation.

Labeled application parameters for watercress calls for a single application of 0.09 lbs a.i/A with a seasonal maximum of three applications totaling 0.266 lbs a.i/acre and a minimum of 7-day

[12] http://www.naturesherbal.com/Watercress.htm and http://edis.ifas.ufl.edu/mv151

reapplication interval. Other input parameters, for the Tier 1 Rice Model include the average K_{oc} (30 L/Kg for parent).

In modeling, parent sulfoxaflor was considered to be the stressor of concern due to the fact that the degradate X-540 is not expected to form in aquatic systems.

b. Results for Modeling

The EECs resulting from the currently proposed three applications is 278 ppb of the TTR which would be parent sulfoxaflor alone because *X-540* is not expected to form in aquatic systems. For a single application, the EEC is 93 ppb TTR while it is 186 ppb TTR following two applications. These initial concentrations estimated by the Tier 1 Rice model assume sulfoxaflor application to watercress growing in a rice paddy containing static water. The only process simulated by the model is partitioning of the applied chemical between the 10-centimeter deep water column and the 1-centimeter deep sediment layer of the paddy. The partitioning is based on the pesticide's partitioning constant (K_d = 0.3 L/Kg calculated by the mode from K_{oc} of 30 L/kg). Other assumptions for the Tier 1 Rice model include:

- All applications are applied at time zero (no application intervals can be simulated);
- The application efficiency is 0.0 (*i.e*., none of the pesticide remains on the watercress plants, which is not a realistic assumption);
- Peak concentrations of the parent occur simultaneously; and
- No degradation occurs in the paddy (the model assumes the residues remain at the initial concentration in the water indefinitely).

Modeling results from Tier 1 Rice model gives concentrations expected in the rice paddy. However, EECs in surface water outside the rice paddy are expected to be affected by many factors. These factors and their impact on modeled EECs are discussed below:

(1) Impact of application efficiency

As stated above, the initial concentrations, in the rice paddy for the TTR of sulfoxaflor are: 93 ppb for single application 186 ppb for two applications, and 278 ppb for three applications. These EECs are based on the assumption that the fraction of amount applied which is intercepted by the crop (*i.e*., the application efficiency) is zero which is not a realistic assumption. **Figure 11** shows the possible impact of application efficiency on the initial concentration in the rice paddy water. Any interception of the applied pesticide (increase in efficiency), by the watercress plant, is expected to reduce EECs on the assumption that the pesticide is reduced by plant intake through leaves before it is washed-off into the soil. In case of sulfoxaflor, the systemic nature of the pesticide increases the chance of this process to occur causing reduction of the EEC values.

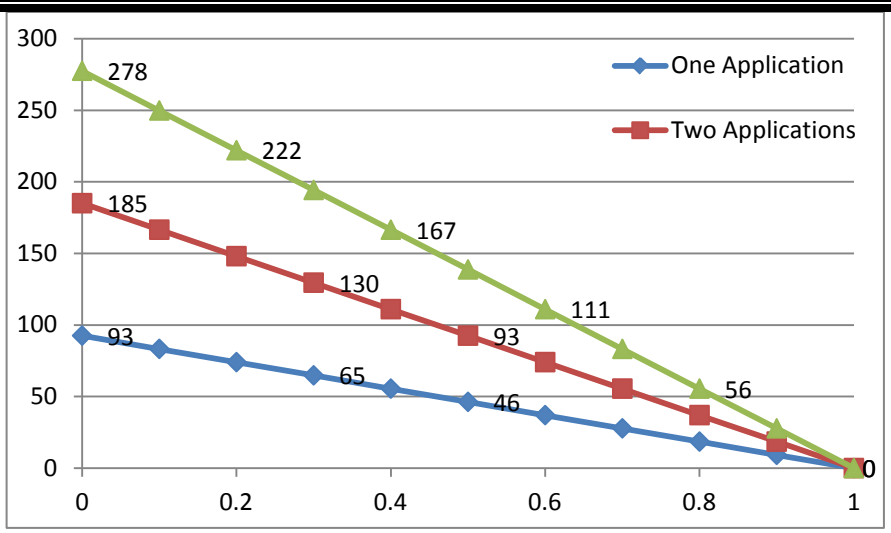


Figure 11. Impact of application efficiency on determined EECS for Surface Water

(2) *Impact of pesticide degradation*

Under field conditions, the initial concentration estimated by the Tier 1 Rice Model (*i.e.*, EECs in the rice paddy) is expected to be reduced by degradation. The impact of degradation on the TTR of sulfoxaflor is only significant only after 100 days and repeated application increased the EECs after 1 year about 10 fold. This is due to observed persistence of parent in water/sediment system (90th % $t_{½}$= 141 days). The effect of degradation on EECs is depicted in **Figure 12.**

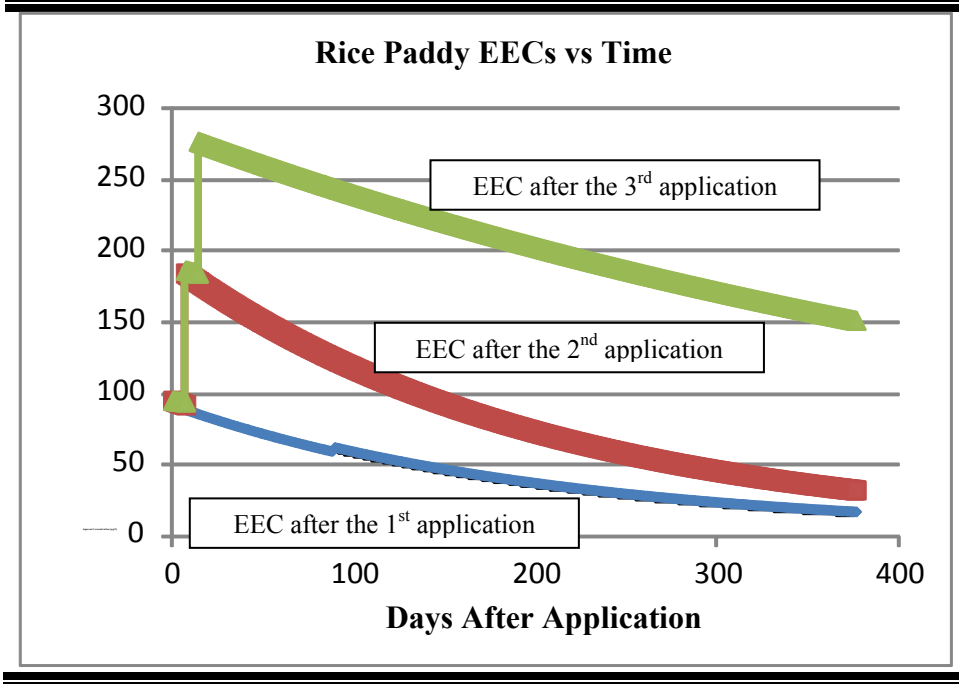


Figure 12. Impact of pesticide degradation on determined EECs in the rice paddy following one (blue line), two (red line) and three (green line) application

In **Figure 12**, the initial EEC value for one application (93 ppb of the TTR) may be reduced by degradation to 15 ppb within a one-year period. The initial EEC value after two applications (184 ppb of the TTR) may be reduced by degradation to 162.6 ppb within a one-year period. Similarly, the initial EEC value following three applications (275 ppb of the TTR) may be reduced by degradation to 149 ppb within a one-year period.

(3) Impact of downstream movement from site in flowing water through watercress cultivated areas

Under actual conditions of watercress cultivation, the amount of pesticide which reaches the stream water will be removed continuously downstream from the site at which it is applied by advection in the flowing water. The rate of removal depends on the rate of flow through the site. River velocity varies from day to day based on the volume of flow and changing cross-sectional area. Typical ranges of velocity vary from zero (at the time of tidal flow direction change) to 7 miles per hour.[13] The Mississippi River ranges from 1.2 to 3 miles per hour depending on the amount of flow and the reach in which it is measured. The pesticide in the flowing water will also spread from the center of mass during the flow. **Figure 13** presents the distance downstream of the center of mass of the applied sulfoxaflor depending on the flow rate of the stream (in miles/hour and in feet/second).

[13] http://hypertextbook.com/facts/2006/NervanaGaballa.shtml

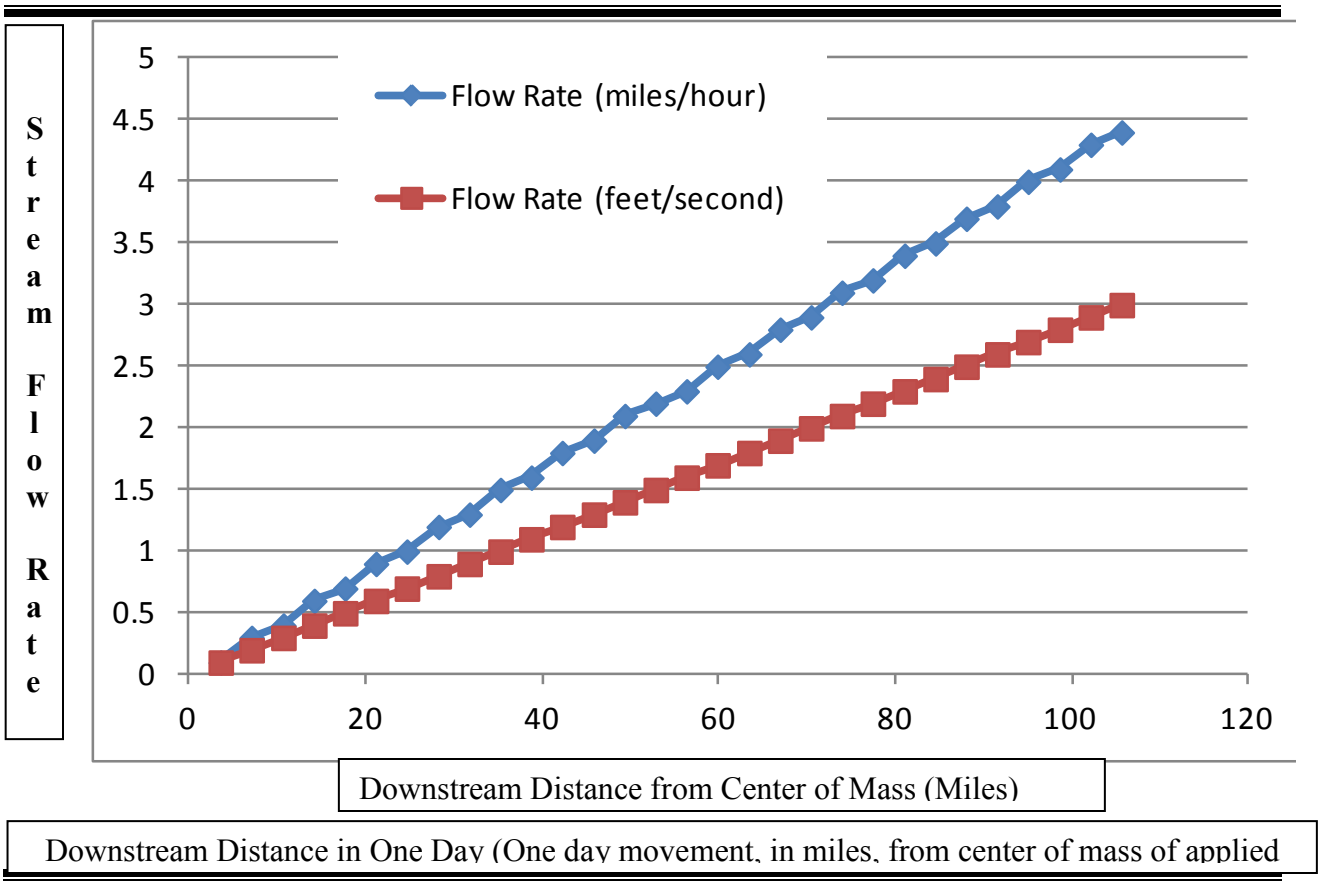


Figure 13. Expected downstream movement, from site of application of sulfoxaflor, in flowing water in one Day

The above presentation suggests that a combination of application efficiency, pesticide degradation and stream flow are expected to produce surface water concentration values lower than the conservative values of 93 to 264 ppb.

(4) Impact of Agronomic Practices

Two important factors can impact EECs arrived at by rice modeling, namely:

(a) Expected usage or acreage that may be treated with the chemical. The EECs from Tier 1 Rice Model are not adjusted for percent crop area (PCA). Lower EECs are expected as a result of such an adjustment due to the fact that reported watercress acreage is limited. In 2007, watercress production totaled nearly 700 acres nationwide, mainly distributed between three states Florida (426 acres), California (151 acres) and Hawaii (15 acres) [14]. Other states where watercress is grown on only few acres include: Alabama, Maryland, Michigan, Pennsylvania, Tennessee and West Virginia. Additionally, the label will further reduce acreage that could potentially be treated with sulfoxaflor as it will limit application of the chemical to "Commercially grown watercress"; and

[14] http://www.agcensus.usda.gov/Publications/2007/Full_Report/usv1.pdf

(b) Known agronomic practices in "commercially grown watercress" are different from those assumed for rice. These practices include[15]:

- Use of flow-through irrigation: water flows through from the top of the crop beds over the surface of beds (having an established gradient) to be collected and pumped back to the top of the beds, *i.e.*, same water is circulated.
- Beds are completely drained prior to, during and after pesticide application
- Depth of flowing water is kept at a maximum depth of one inch.

It is noted that none of these factors were taken in consideration in modeling EECs for sulfoxaflor. However, the most important aspect of the above practices are water reuse (reduce possible contamination for surface waters) and draining of the beds prior to, during and after pesticide application. This limits direct application of the pesticide to water and gives time for its degradation of the parent sulfoxaflor into X-474 reducing the contribution of parent sulfoxaflor to the EECs (i.e., reducing surface water contamination with the stressor "parent sulfoxaflor" as the only expected contaminant would be from parent drift and from X-474 (not considered as part of the stressor in this assessment). In this case, surface water EECs for watercress could be represented by the CA lettuce scenario (**Table 20**).

Table 20. EECs for watercress use when watercress beds are drained prior to, during and after pesticide application sulfoxaflor

Crop (State)	*Crop Group(s)*	*Crop(s)*	*Scenario*	*DATE*	*Peak*	*21-day*	*60-day*
(1) EECs for surface water (ppb)							
Leafy vegetables	CG-4	Lettuce/Celery/ Spinach	CAlettuceSTD	22m04	1.7	1.62	1.55
(2) EECs for pore water (ppb)							
Leafy vegetables	CG-4	Lettuce/Celery/ Spinach	CAlettuceSTD	22m04	1.33	1.33	1.33

b) Aquatic Exposure Monitoring (Field Data)

This is a new pesticide and therefore no data were identified to provide information on aquatic monitoring.

3.2.3 Terrestrial Exposure Assessment

Terrestrial wildlife exposure estimates are typically calculated for bird and mammals, emphasizing a dietary exposure route for uptake of pesticide active ingredients. These exposures

[15] Information is taken from a presentation to EPA by B&W of Florida, a commercial watercress grower.

are considered as surrogates for terrestrial-phase amphibians as well as reptiles. For exposure to terrestrial organisms, such as birds and small mammals, pesticide residues on food items are estimated, based on the assumption that organisms are exposed to a single pesticide residue in a given exposure scenario.

3.2.3.1 . Terrestrial Vertebrate Exposure Modeling

For sulfoxaflor spray applications, estimation of pesticide concentrations in wildlife food items focuses on quantifying possible dietary ingestion of residues on vegetative matter and insects. As described earlier, the EFED terrestrial exposure model T-REX (version 1.5.1) is used to estimate exposures and risks to avian and mammalian species. Input values used for estimating avian and mammalian exposure risks to sulfoxaflor are summarized in **Table 21.**

Table 21. Input parameters used in T-REX v1.5 to determine terrestrial EECs for the maximum sulfoxaflor spray application scenarios.

Input Variable	Parameter Value	Source
Maximum application rate and frequency*	0.133 lb a.i./A x 2 0.090 a.i/A x 3	Product Label
Minimum Application Interval	5-14 days	Product Label
Foliar half-life	12.3 days	Sulfoxaflor residue-decline data (MRID 48755703)

* Crop uses applicable to these use patterns are shown in **Table 4.**

For deriving a sulfoxaflor-specific foliar dissipation rate, an abundance of residue-decline data was available from registrant-submitted field residue trials (MRID 48755703). In selecting data sets for calculating the foliar dissipation half life values, guidelines provided in the T-REX User's Guide was followed.[16] Specifically, residue-decline data sets needed to meet the following criteria in order to be considered for half life calculation:

1. Day 0 measurement of residues available
2. At least 3 measurement times with residues above the limit of detection
3. R^2 values (ln concentration vs. time) of 0.7 or higher
4. Statistical significance of regression coefficient of 0.1 or lower

Based on these criteria, a total of 44 foliar DT_{50} values were available for sulfoxaflor (**Appendix B)**. These DT_{50} values consisted of measurements on a variety of crops and plant matrices (*e.g.*, foliage, fruit, seeds, grains and roots. In situations were multiple trials were available within a crop and crop matrix (*e.g.*, multiple values for head lettuce), the DT_{50} values were averaged. The resulting 25 DT_{50} values averaged within a crop matrix are shown in **Figure 14**. These foliar DT_{50} values ranged from 1.8 to 29, with a calculated 90th percentile DT_{50} of 12.3 days based on log transformed values.

[16] http://www.epa.gov/oppefed1/models/terrestrial/trex/t_rex_user_guide.htm

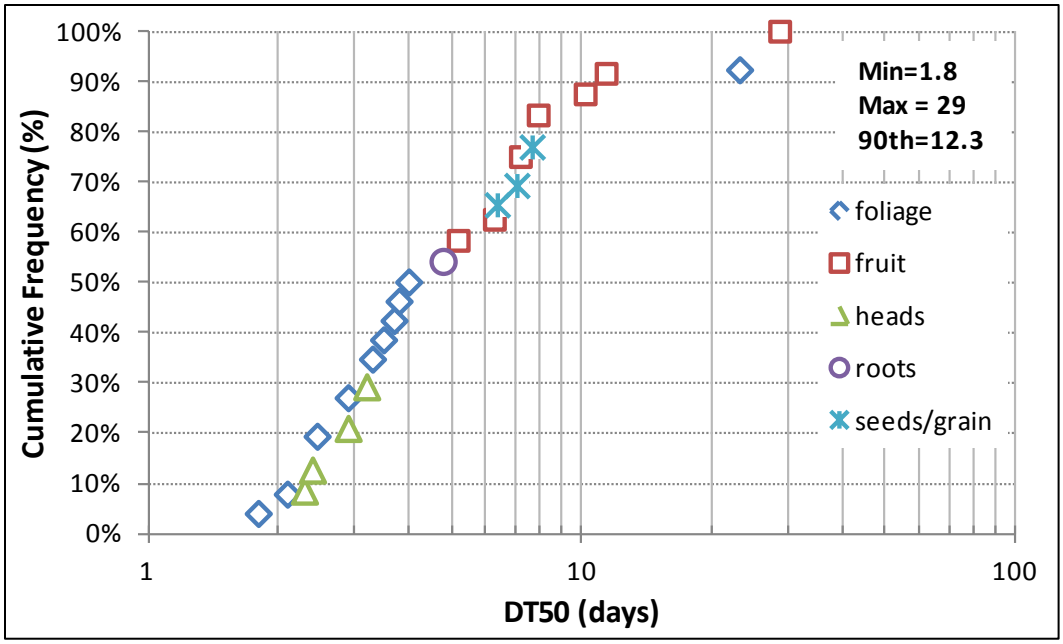


Figure 14. Summary of foliar dissipation half life (DT50) values for sulfoxaflor

It appears from examination **Figure 14** that the crop matrix exerts some influence on the DT_{50} values, with residues measured in fruits and seeds/grains generally having the longest DT_{50} values. With one exception, average crop matrix DT_{50} values measured in plant foliate (leaves, whole plant, straw, hay) are about 4 days or less.

3.2.3.2. Terrestrial Exposure Monitoring (Field Data)

Sulfoxaflor is a new pesticide and therefore, no monitoring data were identified to provide information on chemical concentrations in terrestrial ecosystems. Experimental data documenting residues in plant tissues relevant to exposure of bees to sulfoxaflor are described in **Section 5.1.**

3.2.3.3. Non-Target Plant Exposure Assessment

Tier I seedling emergence and vegetative vigor toxicity tests did not establish EC_{25} estimates, *i.e.*, the EC_{25} values were higher than the highest treatment rate tested, for sulfoxaflor. Specifically, no detrimental effects ≥25% were observed for any test species at rates up to 0.357 lb a.i/A (MRID 47832425 and 47832427) which is approximately 2.5X the maximum single application rate of 0.133 lb a.i/A). Furthermore, NOAEC values for terrestrial plants also exceeded the maximum single application rate of sulfoxaflor tested. Therefore, no exposure modeling was conducted for terrestrial plants since non-listed and listed species LOC of 1.0 could not be exceeded.

4. Ecological Effects Characterization

In screening-level ecological risk assessments, effects characterization describes the types of effects a pesticide can produce in an aquatic or terrestrial organism. This characterization is based on registrant-submitted studies that describe acute and chronic effects toxicity information for various aquatic and terrestrial animals and plants. A summary of the results of the registrant-submitted toxicity studies used to characterize effects for this risk assessment is provided in **Appendix C** (all taxa except bees) and **Appendix D** (for bees). Toxicity testing reported in this section does not represent all species of birds, mammals, or aquatic organisms. Only a few surrogate species for both freshwater fish and birds are used to represent all freshwater fish (2000+) and bird (680+) species in the United States. For mammals, acute studies are usually limited to Norway rat or the house mouse. Estuarine/marine testing is usually limited to a crustacean, a mollusc, and a fish. Also, neither reptiles nor amphibians are tested. The risk assessment assumes that avian serve as a surrogate for the terrestrial-phase amphibians and reptiles. This assessment also assumes that freshwater fish serve as a surrogate for aquatic-phase amphibians.

4.1 Aquatic Effects

A summary of toxicity data for the most sensitive species within each taxonomic group of aquatic organisms is provided in **Table 22**; the most sensitive tested species in each of the taxonomic groups is shown in bold**.** All submitted data for sulfoxaflor were with TGAI; no technical end product (TEP) data were submitted with aquatic organisms.

Table 22. Summary of sulfoxaflor toxicological endpoints for aquatic organisms

Taxa	Species Tested	Toxicity Exposure[(1)]	Toxicological Endpoint (mg a.i./L)	MRID (Classification)
Freshwater Fish	Rainbow trout (*Oncorhynchus mykiss)*	Acute	LC_{50} (96-hr): >387	47832111 (Acceptable)
	Common carp (*Cyprinus carpio)*		LC_{50} (96-hr): >402	47832113 (Acceptable)
	Bluegill sunfish (*Lepomis macrochirus*)		**LC_{50} (96-hr): >363**	4783212 (Supplemental)
	Rainbow trout (*Oncorhynchus mykiss)*	Acute (X11719474)	LC_{50} (96-hr): >478	47832105 (Acceptable)
	Fathead minnow (*Pimephales promelas)*	Chronic	**30-d NOAEC (ELS): 0.66 (reduced dry wt.)**	47832126 (Supplemental)
Freshwater Invertebrate	**Water flea (*Daphnia magna)***	Acute	**EC_{50} (48-hr): >400**	47832114 (Acceptable)
		Acute (X11719474)	EC_{50} (48-hr): >205	47832106 (Acceptable)
		Chronic	**NOAEC (21-day): 50.5 (reduced reproduction)**	47832127 (Acceptable)
Marine/Estuarine Fish	**Sheepshead minnow (*Cyprinodon variegatus*)**	Acute	**LC_{50} (96-hr): 266**	47832110 (Acceptable)

Taxa	Species Tested	Toxicity Exposure[1]	Toxicological Endpoint (mg a.i./L)	MRID (Classification)
		Chronic	**NOAEC(30-d): 1.2 (reduced length)**	47832129 (Acceptable)
Marine/Estuarine Invertebrate	**Mysid shrimp (*Americamysis bahia*)**	Acute Chronic	**LC_{50} (96-hr): 0.64** **NOAEC: 0.11 (time to first brood)**	47832117 (Acceptable) 47832128 (Acceptable)
	Eastern oyster (*Crassostrea virginica)*	Acute	EC_{50} (96-hr): 86.5	47832115 (Acceptable)
Freshwater Benthic Invertebrates	Midge (*Chironomus dilutus*)	Subchronic	NOAEC (10-d): 0.099 mg a.i/L pore water (dry wt.) NOAEC (10-d): 0.049 mg a.i/kg dry sediment (dry wt.)	47832109 (Acceptable)
	Midge (*Chironomus riparius)*	Chronic	**NOAEC (28-d): 0.037 mg a.i/L pore water (emergence)** **NOAEC (28-d): 0.05 mg a.i/kg dry sediment (emergence)**	Gerke A (2009) (Supplemental)
Aquatic Non-vascular Plants	**Freshwater diatom (*Navicula pelliculosa)***		**EC_{50} (96-h): 81.2 (Biomass)** **NOAEC (96-h): 3.54 (R,Y,B)** [2]	47832123 (Acceptable)
	Green alga *(Pseudokirchneriella subcapitata)*		EC_{50} (96-h): >101 (R,Y,B) NOAEC (96-h): 101 (R,Y,B)	47832121 (Acceptable)
	Bluegreen alga (*Anabaena flos-aquae)*		EC_{50} (72-h): 83.8 (Y) NOAEC (72-h): 12.0 (G,Y,B)	47832124 (Supplemental)
	Marine diatom (*Skeletonema costatum*)		EC_{50} (96-h): >103 (R,Y,B) NOAEC (96-h): 103 (R,Y,B)	47832122 (Supplemental)
Aquatic Vascular	**Duckweed *(Lemna gibba)***		**EC_{50} (7-d): >99** **NOAEC (7-d): 99 (dry wt, frond count)**	47832125 (Acceptable)

[1] Test substance is TGAI with purities > 95%.
[2] R= growth rate; Y= yield; B= biomass integral; Toxicity values shown in bold are used for risk estimation
The most sensitive endpoints shown in **bold** were used for risk estimation.

4.1.1 Acute Toxicity to Fish

Sulfoxaflor is classified as practically non-toxic on an acute exposure basis, with 96-h LC_{50} values of >400 mg a.i./L for all three freshwater fish species tested (bluegill, *Lepomis macrochirus*; rainbow trout, *Oncorhynchus mykiss*; and common carp, *Cyprinus carpio*; MRID 47832112, 47832111, and 47832113, respectively). Mortality was 5% or less at the highest test

treatments in each of these studies. Treatment-related sublethal effects included discoloration at the highest treatment concentration (100% of fish at 400 mg a.i./L for bluegill) and fish swimming on the bottom (1 fish at 400 mg a.i./L for rainbow trout). No other treatment-related sublethal effects were reported. For an estuarine/marine sheepshead minnow (*Cyprinodon variegatus*; MRID 47832110), sulfoxaflor was also practically non-toxic with an LC_{50} of 288 mg a.i./L. Sublethal effects included loss of equilibrium or lying on the bottom of aquaria at 200 and 400 mg a.i./L. The primary degradate of sulfoxaflor (X474) is also classified as practically non-toxic to rainbow trout on an acute exposure basis (96-h LC_{50} >500 mg a.i./L; MRID 47832105).

4.1.2 Chronic Toxicity to Fish

Adverse effects from chronic exposure to sulfoxaflor were examined with two fish species (fathead minnow, *Pimephales promelas,* MRID 47832126; and sheepshead minnow; MRID 47832129) during early life stage toxicity tests. For fathead minnow, the 30-d NOAEC is 5 mg a.i./L based on a 30% reduction in mean fish weight relative to controls at the next highest concentration (LOAEC=10 mg a.i./L). No statistically significant and/or treatment-related effects were reported for hatching success, fry survival and length. For sheepshead minnow, the 30-d NOAEC is 1.3 mg a.i./L based on a statistically significant reduction in mean length (3% relative to controls) at 2.5 mg a.i./L. No statistically significant and/or treatment-related effects were reported for hatching success, fry survival and mean weight.

4.1.3 Acute Toxicity to Aquatic Invertebrates

The acute (water column) toxicity of sulfoxaflor was evaluated for one freshwater species (waterflea, *Daphnia magna;* MRID 47832114) and two saltwater species (mysid shrimp, *A. bahia;* MRID 47832117 and Eastern oyster, *Crassostrea virginica*; MRID 47832115). For *D. magna*, the 48-h EC_{50} is >400 mg a.i./L, the highest concentration tested . For Eastern oyster, new shell growth was significantly reduced at 120 mg a.i./L (75% reduction relative to control). The 96-h EC_{50} for shell growth is 93 mg a.i./L. No mortality occurred at any test concentration. Mysid shrimp are the most acutely sensitive invertebrate species tested with sulfoxaflor based on water column only exposures, with a 96-h LC_{50} of 0.67 mg a.i./L. The primary degradate of sulfoxaflor (X474) is also classified as practically non-toxic to *D. magna* (EC_{50} >240 mg a.i./L; MRID 47832106).

4.1.4 Chronic Toxicity to Aquatic Invertebrates

The chronic effects of sulfoxaflor to *D. magna* were determined in a semi-static system over a period of 21 days to nominal concentrations of 6.25, 12.5, 25, 50 and 100 mg a.i./L (MRID 47832127). Adult mortality, reproduction rate (number of young), length of the surviving adults, and days to first brood were used to determine the toxicity endpoints. In this flow through study, the test substance was stable and the mean-measured concentrations approximated the nominal concentrations (100-101% of nominal); therefore, the biological endpoints are reported as nominal concentrations. No treatment-related effects on adult mortality or adult length were observed. The reproduction rate and days to first brood were significantly ($p<0.05$) different in

the 100 mg a.i./L test group (40% reduction in mean number of offspring; 35% increase in time to first brood). No significant effects were observed on survival, growth or reproduction at the lower test concentrations. The 21-day NOAEC and LOAEC were determined to be 50 and 100 mg a.i./L, respectively.

The chronic effects of sulfoxaflor to mysid shrimp were determined in a flow-through system over a period of 28 days to nominal concentrations of 0.063, 0.13, 0.25, 0.50 and 1.0 mg a.i./L (MRID 47832128). Mortality of parent (F_0) and first generation (F_1), reproduction rate of F_0 (number of young), length of the surviving F_0 and F_1, and days to first brood by F_0 were used to determine the toxicity endpoints. Complete F_0 mortality (100%) was observed at the highest test concentration of 1.0 mg a.i./L within 7 days; no treatment-related effects on F_0/F_1 mortality, F_0 reproduction rate, or F_0/F_1 length were observed at the lower test concentrations, which is somewhat unexpected given the reported acute LC_{50} 0f 0.67 mg a.i./L described previously. The days to first brood by F_0 were significantly ($p<0.05$) different in the 0.25 and 0.50 mg a.i./L test groups (both means: 17.0 days to first brood) relative to the controls (mean: 17.8 days to first brood), although this represents just a 4.5% increase relative to controls. No significant effects on days to first brood by F_0 were observed at the lower test concentrations. The 28-day NOAEC and LOAEC were determined to be 0.11 mg and 0.25 mg a.i./L, respectively.

Although the chemical properties of sulfoxaflor (*i.e.*, low K_{ow}, low partitioning to solids) would not result in a requirement for submitting sediment toxicity testing, the subchronic toxicity of sulfoxaflor to benthic invertebrates via sediment exposure was investigated for larvae of the freshwater chironomid, *Chironomus dilutus* (MRID 47832109). For risk estimation, toxicity endpoints based on concentrations in pore water and sediment are used. Following a 10-day sub-acute exposure to C^{14}-labeled sulfoxaflor administered in spiked sediments, 43% and 0% survival was observed at mean sediment concentrations of 0.17 and 0.36 mg a.i./kg dry sediment, respectively. Analysis of overlying water samples taken from the 1.0 mg a.i./L treatment via HPLC/MS/MS indicate that nearly all of the TRR was parent compound over the 10-day study duration (only 3% was detected as X-474 by day 10). Survival in all other treatments (0.025 to 0.09 mg a.i./kg dry sediment and controls) was 93% or greater. The NOAEC based on dry weight is 0.049 mg TRR/kg dry sediment with a 31% reduction in mean dry weight occurring in the next highest treatment (0.09 mg TRR/kg dry sediment). This NOAEC is equivalent to 0.099 mg a.i./L (mean-measured) in pore water.

The chronic toxicity of sulfoxaflor to midge larvae (*C. riparius*) in whole sediment was determined using spiked water dosing. Midges were exposed to sulfoxaflor applied to the overlying water in a static system over a period of 28 days to nominal concentrations of 0.065, 0.13, 0.25, 0.50 and 1.0 mg a.i./L. Emergence, development rate and survival were used to determine the toxicity endpoints. The TRR in the overlying water decreased to about 72-81% of nominal after 28 days which was attributed to the test substance being incorporated into the pore water and sediment based on analytical results from the study. Approximately two-thirds of the residues in the overlying water of the 0.100 mg a.i./L treatment were determined to be sulfoxaflor, while X474 comprised the remaining third; therefore, the biological endpoints are reported as mean-measured TRR concentrations (0.00142, 0.00286, 0.00604, 0.0112, 0.0225, 0.0455 and 0.0949 mg TRR/L overlying water). Emergence was significantly lower at 0.0949

mg TRR/L (mean: 70%) relative to controls (mean: 91%). No treatment-related effects on development rate were observed. The 28-day NOAEC was determined to be 0.046 mg TRR/L for overlying water, 0.037 mg TRR/L for pore water, and 0.05 mg/kg for dry sediment. Since effects on midge reproduction were not quantified per USEPA Agency-wide guidelines for chronic sediment toxicity testing (USEPA, 2000), this test is classified as supplemental.

4.1.5 Toxicity to Aquatic Plants

Sulfoxaflor exhibited relatively low toxicity to aquatic non-vascular plants. The most sensitive aquatic nonvascular plant is the freshwater diatom, *Navicula pelliculosa*, with a 96-h EC_{50} of 81.2 mg a.i./L (MRID 47832123) Similarly, sulfoxaflor was not toxic to the freshwater vascular aquatic plant, *Lemna gibba*, up to the limit amount, as indicated by a 7-d EC_{50} for frond count, dry weight and growth rate of >100 mg a.i./L (MRID 47832125) with no significant adverse effects on these endpoints observed at any treatment concentration.

4.2 Terrestrial Effects

A summary of toxicological endpoints for terrestrial organisms exposed to sulfoxaflor is provided in **Table 23**.

Table 23. Summary of sulfoxaflor toxicological endpoints for terrestrial organisms.

Taxa	Species	Type of Toxicity (Purity)[(1)]	Toxicological Endpoint	MRID
Birds	Bobwhite Quail *(Colinus virginianus)* **Zebra finch (*Poephila guttata)***	Acute (oral) (95.6%; TGAI)	LD_{50}: 676 mg/kg bw **LD_{50}: >80 mg/kg bw**	47832101 (Acceptable) 47832072 (Supplemental)
	Bobwhite Quail *(Colinus virginianus)*	Acute (oral) X11719474 (99.5%)	LD_{50}: > 2,250 mg/kg bw	47832073 (Acceptable)
	Bobwhite Quail *(Colinus virginianus)* **Mallard duck (*Anas platyrhynchus)***	Subacute (dietary) (95.6%; TGAI)	LC_{50}(5-d): > 5,620 ppm **LC_{50}(5-d): >5,620 ppm**	47832074 (Acceptable) 47832104 (Acceptable)
	Bobwhite Quail *(Colinus virginianus)* **Mallard duck (*Anas platyrhynchus)***	Chronic (95.6%; TGAI)	NOAEL (20 wk): 1,000 ppm (81 mg ai/kg bw/d) **NOAEL (20 wk): 200 ppm (26 mg ai/kg bw/d)**	47832119 (Acceptable) 47832120 (Acceptable)
Mammals	Rat *(Rattus norvegicus)*	Acute (oral) (95.6%; TGAI)	LD_{50} 1000 mg ai/kg bw (female)	47832144 (Acceptable)
	Mouse *(Mus musculus)*		LD_{50} 750 mg ai/kg bw	47832040 (Acceptable)

Taxa	Species	Type of Toxicity (Purity)[1]	Toxicological Endpoint	MRID
	Rat (*Rattus norvegicus)* Rat (*Rattus norvegicus)*	Acute (oral) GF-2372 TEP (40%)	LD_{50} >2000 mg ai/kg bw	47832505 (Acceptable)
		Acute (oral) GF-2032 TEP (22%)	LD_{50} >5000 mg ai/kg bw	47832407 (Acceptable)
		Chronic dietary (95.6%; TGAI)	**NOAEL (two generation): 100 ppm (6.07 mg ai/kg bw) (decreased neonatal survival)**	47832142 (Acceptable)
Terrestrial Invertebrates	**Honey bee, adult (*Apis mellifera)***	Acute (contact) TGAI	LD_{50} (72-h): 0.379 ug a.i./bee	47832102 (Acceptable)
		Acute (contact) TEP: GF-2032-SC	**LD_{50} (48-h): 0.130 ug a.i./bee**	47832419 (Acceptable)
		Acute (contact) TEP: GF-2372-WG	LD_{50} (48-h): 0.224 ug a.i./bee	47832511 (Acceptable)
		Acute (oral) TGAI	LD_{50} (48-h): 0.146 ug a.i./bee	47832103 (Acceptable)
		Acute (oral) TEP: GF-2032-SC	**LD_{50} (48-h): 0.052 ug a.i./bee**	47832417 (Acceptable)
		Acute (oral) X11719474	LD_{50} (96-h): >100 ug a.i./bee	47832107 (Acceptable)
		Acute (oral) X11721061	LD_{50} (48-h): >104 ug a.i./bee	48445809
		Acute foliar residue (TEP: GF-2372-WG)	24-h aged residue mortality: 14% (0.089 lb ai/A or 100 g ai/ha) 15% (0.178 lb ai/A or 200 g ai/ha)	47832512 (Acceptable)
		Acute foliar residue (TEP: GF-2032-SC)	3-h aged residue mortality: 4% (200 g ai/ha)	47832420 (Acceptable)
	Honey bee, larvae (*Apis mellifera)*	Chronic, single dose (TGAI) **Chronic, repeated dose (TGAI)**	NOAEC (7-d): 0.2 µg a.i./bee larvae **NOAEC (7-d): 0.02 µg a.i./bee larvae**	48755602 (Supplemental) 48755603 (Supplemental)
	Bumble bee, adult (*Bombus terrestris)*	Acute (contact) (TEP: GF-2032-SC)	LD_{50} (72-h): 7.55 µg a.i./bee	47832418 (Supplemental)
		Acute (oral) (TEP: GF-2032-SC)	LD_{50} (72-h): 0.027 µg a.i./bee	47832418 (Supplemental)
Terrestrial plants	Multiple species	Tier 1 – Seedling Emergence (TEP: GF-2032-SC)	EC_{25} (21-d): > 0.357 lb ai/A (>400 g ai/ha) NOAEC = 0.357 lb ai/A (400 g ai/ha)	47832427 (Acceptable)

Taxa	Species	Type of Toxicity (Purity)[1]	Toxicological Endpoint	MRID
Terrestrial plants	Multiple species	Tier 1/2 – Vegetative Vigor (TEP: GF-2032-SC)	EC_{25} (21-d): > 0.178 lb ai/A (>200 g ai/ha) NOAEC = 0.178 lb ai/A (200 g ai/ha)	47832425 (Supplemental)

The most sensitive endpoints shown in bold were used for risk estimation.

4.2.1 Toxicity to Birds

Based on an acute oral LD_{50} of 676 mg a.i./kg bw for bobwhite quail (*Colinus virginianus*), sulfoxaflor is considered slightly toxic to birds on an acute oral exposure basis (MRID 47832101). The acute oral LD_{50} could not be determined for the passerine zebra finch (*Taeniopygia guttata*; MRID 47832072) due to regurgitation at treatments above 29 mg a.i./kg bw). In this study, 40% mortality was observed at the highest dose (200 mg a.i./kg bw) with no mortality occurring at lower doses. In the controls and lowest dose (29 mg a.i./kg bw), no birds regurgitated. A dose-dependent increase in the rate of regurgitation was observed at higher treatments (1/10 at 49 mg a.i./kg bw; 2/10 at 80 mg a.i./kg bw; 7/10 at 132 mg a.i./kg bw; 10/10 at 200 mg a.i./kg bw). Sublethal effects at 49 mg a.i./kg bw and above included ruffled appearance, loss of coordination, lower limb weakness, prostrate posture, loss of righting reflex, convulsions and lethargy). The LD_{50} to estimated to be >80 mg a.i./kg bw based on the lowest level at which ≤20% birds regurgitated and no mortality occurred. Thus, even one assumes all the birds that regurgitated their dose would have died, the LD_{50} would be somewhere between 80 and 132 mg a.i./kg bw (20% and 70% regurgitation).

On a subacute, dietary exposure basis, sulfoxaflor is classified as practically nontoxic to birds, with 5-d LC_{50} values of >5620 mg/kg-diet for mallard ducks (*Anas platyrhynchus*) and bobwhite quail (MRID 47832104 and 47832074, respectively). The NOAEL from these studies is 5620 mg/kg-diet as no treatment related mortality of sublethal effects were observed at any treatment. Similarly, the primary degradate (-474) is classified as practically nontoxic to birds on an acute oral exposure basis with a LD_{50} of >2250 mg a.i./kg bw (MRID 47832073).

In two chronic, avian reproductive toxicity studies, the 20-week NOAELs ranged from 200 mg/kg-diet (mallard, MRID 47832120, highest concentration tested) to 1000 mg/kg-diet (bobwhite quail, highest concentration tested). No treatment-related adverse effects were observed at any test treatment in these studies.

4.2.2 Toxicity to Mammals

In an acute oral 'up-down' toxicity study conducted according to Organization for Economic Cooperation and Development (OECD) protocol (MRID 47832144), a series of fasted, young adult rats (6/sex) were given a single oral dose of sulfoxaflor XDE-208 in 0.5% aqueous methylcellulose at either 630 mg/kg bw (2 males, 2 females), 1000 mg/kg bw (2 males, 3 females), 1580 mg/kg bw (1 male, 1 female) or 2000 mg/kg bw (1 male). Based on an estimated LD_{50} of 1000 mg/kg bw, and an assumed standard deviation of 0.2, a starting dose level of 630 mg/kg bw of sulfoxaflor was administered to one male and one female rat. Since both animals

survived, the second animals received a higher dose at 1000 mg/kg bw. Clinical signs included muscle tremors, twitches, tonoclonic convulsions, decreased activity, decreased reactivity, decrease fecal output, eyelids partially closed (ptosis), hair standing up (piloerection), labored respiration, soiling, increased salivation, increased lacrimation, lack of coordination, hypersensitivity to stimuli, , and decreased responsiveness to touch. Mortality was observed at ≥1000 mg/kg bw. The male and female acute LD_{50} values were estimated to be 1405 and 1000 mg/kg bw, respectively.

In an acute oral up-down toxicity study conducted according to OECD guidelines (MRID 47832040), a series of fasted, young adult male mice were given a single oral dose of sulfoxaflor 95.6% TGAI n 0.5% aqueous methylcellulose at either 560 mg/kg bw (1 animal), 750 mg/kg bw (3 animals) or 1000 mg/kg bw (1 animal). Clinical signs noted prior to death included muscle twitches, tremors, and convulsions, increased reactivity to stimuli, and increased responsiveness to touch. No gross internal findings were observed at necropsy. The oral LD_{50} was determined to be 750 mg a.i./kg bw.

The acute, oral toxicity of formulated products GF-2372 and GF-2032 was also evaluated with the rat at limit doses of 2000 and 5000 mg a.i./kg bw (MRID 47832505 and 47832407, respectively). In both studies, no mortality or deleterious effects on body weight occurred at the limit doses. Rats exposed to GF-2372 showed sublethal effects including facial staining, ano-genital staining and/or reduced fecal volume; all animals recovered with normal behavior at 8 days. No sublethal signs of toxicity were observed with rats administered 5000 mg a.i./kg bw GF-2032.

In a chronic two-generation dietary reproduction toxicity study, sulfoxaflor (95.6% purity) was administered to Sprague Dawley rats (27/sex/dose group) at concentrations of 0, 25, 100 or 400 ppm in the diet for approximately ten weeks prior to breeding, and continuing through breeding, gestation and lactation for two generations. In-life parameters included clinical observations, feed consumption, body weights, estrous cyclicity, reproductive performance, pup survival, pup body weights, puberty onset and anogenital distance. In addition, post-mortem evaluations included gross pathology and organ weights in weanlings, toxicokinetic analyses, gross pathology, organ weights, oocyte quantitation and sperm count, motility and morphology, and histopathology, in adults. Systemic effects in parents consisted of only increased absolute and relative liver weights; these effects are not considered to be ecologically relevant and are not considered for the wild mammal risk assessment. Reproductive effects were limited to 400 ppm and comprised slightly decreased neonatal survival in both generations (81.2 vs. 95.4% in controls); this in turn led to a lower percentage of live pups up to culling on post-natal day 4 (PND 4). In addition, there was an apparent treatment-related delay in preputial separation (PPS) for 400 ppm F_1 males. This external marker of male puberty onset is androgen dependent, but the underlying reason for how sulfoxaflor induced this finding is not known. There were no effects on the onset of puberty or any other parameter of reproductive performance or offspring growth and survival at 25 or 100 ppm. Toxicokinetic data from lactation day 4 (LD 4) dams and culled PND 4 pups in the second generation show dose-proportional systemic exposure to sulfoxaflor in dams and their offspring. The LOAEL for reduced neonatal survival is 400 ppm (24.6 mg/kg/day) and the NOAEL is 100 ppm (6.07 mg/kg/day).

4.2.3 Toxicity to Bees

Sulfoxaflor is considered highly toxic to the honeybee, *Apis mellifera,* with an acute contact LD_{50} value of 0.379 µg ai/bee (TGAI; MRID 47832102) and 0.130 µg ai/bee (formulated product GF-2032-SC; MRID 47832419). Sulfoxaflor was also highly toxic on an acute oral basis (LD_{50} value of 0.146 µg ai/bee (TGAI, MRID 47832103) and 0.052 µg ai/bee (formulated product GF-2032-SC, MRID 47832417). Conversely, the primary degradate (X474) is classified as practically nontoxic to bees on an acute contact basis with an acute contact LD_{50} of >100 ug/bee (MRID 47832107). Based on aged residues of GF-2032-SC on alfalfa at 200 g/ha, <5% mortality occurred following exposure to alfalfa aged from 3 to 24 hours (MRID 47832420). With the GF-2372-WG formulation, up to 15% mortality occurred following exposure to alfalfa aged from 3-24 hours (MRID 47832512).

For the bumble bee, *Bombus terrestris*, sulfoxaflor (formulated product, GF-2032-SC) was much less toxic compared to honeybee on an acute contact basis (LD_{50} of 7.55 µg ai/bee, MRID 47832418) compared to 0.130 µg ai/bee for the honeybee). However, based on acute oral exposure, the toxicity of sulfoxaflor formulated product (GF-2032-SC) was similar among the bumble bee and honeybee (72-h LD_{50} of 0.027 µg ai/bee; MRID 47832511 and 48-h LD_{50} of 0.052 µg ai/bee, respectively).

4.2.4 Toxicity to Terrestrial Plants

Sulfoxaflor did not exhibit treatment-related signs of toxicity to terrestrial plants at or above the proposed maximum seasonal application rate on cotton (200 g/ha) based on vegetative vigor and seedling emergence tests (MRID 47832425 and 47832427, respectively).

5. RISK CHARACTERIZATION

Risk characterization provides the final step in the risk assessment process. In this step, exposure and effects characterization are integrated to provide an estimate of risk relative to established levels of concern (LOCs; **Section 5.1**). The results are then interpreted for the risk manager through a risk description and synthesized into an overall conclusion (**Section 5.2**). In addition, the risk description also contains a discussion of relevant sources of uncertainty in the risk assessment and sensitivity of the risk assessment findings to important methodological assumptions.

5.1 Risk Estimation - Integration of Exposure and Effects Data

As discussed in the problem formulation, risk characterization integrates EECs and toxicity estimates and evaluates the likelihood of adverse ecological effects to non-target species. For sulfoxaflor, a deterministic approach is used to evaluate the likelihood of adverse ecological effects to non-target species. In this approach, RQs are calculated by dividing EECs by acute and chronic ecotoxicity values for non-target species.

Risk Quotient (RQ) = Exposure Estimate/Toxicity Estimate

RQs are then compared to LOCs. These LOCs are criteria used to indicate potential risk to non-target organisms and the need to consider regulatory action. LOC exceedence is interpreted to mean that the labeled use (or proposed use) of the pesticide has the potential to cause adverse effects on non-target organisms. LOCs currently address the following risk presumption categories:

Animals:

- **acute risk** - potential for acute risk to non-target organisms which may warrant regulatory action in addition to restricted use classification,
- **acute risk, restricted use** – potential for acute risk to non-target organisms, but may be mitigated through restricted use classification,
- **acute risk, listed species** – listed species may be potentially affected by use,
- **chronic risk** – potential for chronic risk may warrant regulatory action, listed species may potentially be affected through chronic exposure,

Plants

- **non-listed plant risk** - potential for effects in non-target (non-endangered) plants, and
- **listed plant risk** – potential for effects in endangered plants.

Risk presumptions, along with the calculation of the corresponding RQs and LOCs, are tabulated below:

Table 24. Risk Presumptions for Aquatic Animals

Risk Presumption	RQ	LOC
Acute Risk	EEC/LC_{50} or EC_{50}	0.5
Acute Restricted Use	EEC/LC_{50} or EC_{50}	0.1
Acute Endangered Species	EEC/LC_{50} or EC_{50}	0.05
Chronic Risk	EEC/NOAEC	1

Table 25. Risk Presumptions for Terrestrial Vertebrate Animals

Risk Presumption	RQ	LOC
Acute Risk	Diet-based EEC/LC_{50} or Dose-based EEC/LD_{50}	0.5
Acute Restricted Use	Diet-based EEC/LC_{50} or Dose-based EEC/LD_{50} (or LD_{50} < 50 mg/kg)	0.2
Acute Endangered Species	Diet-based EEC/LC_{50} or Dose-based EEC/LD_{50}	0.1
Chronic Risk	Diet or Dose-based EEC/Diet or Dose-based NOAEC	1

Table 26. Risk Presumptions for Terrestrial Invertebrate Animals

Risk Presumption	RQ	LOC
Acute Risk to Bees[(1)]	EEC (adult contact) / LD_{50} (adult contact)	
	EEC (adult or larvae oral) / LD_{50} (adult or larvae oral)	0.4
Chronic Risk to Bees [(1)]	EEC (adult or larvae oral) / NOAEC or LD10 (adult or larvae)	1

[(1)] RQ and LOC values for bees are proposed values (USEPA 2012).

Table 27. Risk Presumptions for Plants

Risk Presumption	RQ	LOC
Terrestrial Plants in Terrestrial and Semi-Aquatic Areas:		
Non-Endangered Species	EEC[(1)]/EC_{25}	1
Endangered Species	EEC/EC_{05} or NOAEC	1
Aquatic Plants:		
Non-Endangered Species	EEC[(2)]/EC_{50}	1
Endangered Species	EEC/EC_{05} or NOAEC	1

5.1.1. Risks to Non-Target Aquatic Animals

Acute and chronic risks to aquatic animals are first estimated based on the maximum aquatic EECs determined from all 51 crop exposure scenarios modeled combined with the most sensitive endpoint within each taxonomic group, as identified in **Table 22**. For screening purposes, this initial comparison is based on the total residues of interest (parent +X-474+X-540). If the maximum RQ value did not exceed the applicable LOC, then no further risk estimation was conducted and a low potential for risk was presumed. If maximum RQ value exceeded the acute

or chronic risk LOC, then RQ values re-calculated using the refined EECs with parent and X-540 constituents, which are considered the residues of toxicological concern.

5.1.1.1. Fish and Invertebrates: Water Column Exposure

Sulfoxaflor is classified as practically non-toxic to freshwater and saltwater fish on an acute exposure basis. As a result, maximum acute and chronic RQ values for freshwater and saltwater fish determined with the crop exposure scenario producing the highest aquatic EECs (NC Cotton) are one to three orders of magnitude below the listed and non-listed species LOC values of 0.5 and 0.05, respectively (**Table 28**).

Table 28. Maximum acute and chronic risk quotients for freshwater and saltwater fish based on total residues of interest

Use Category	Crop Scenario	Peak EEC[1] (mg/L)	60-day EEC[1] (mg/L)	Acute RQ [2]		Chronic RQ [3]	
				FW	SW	FW	SW
Cotton	NC Cotton	0.0530	0.0527	<0.0001	0.0002	0.08	0.04

[1] For screening purposes, these EECs are based on total residues of interest (parent + X-474 + X-540).
[2] Acute RQ values for freshwater and saltwater fish are based on the peak EEC / LC_{50} values of >363 mg a.i./L (bluegill sunfish) and 266 mg a.i./L (sheepshead minnow), respectively (see **Table 22**)
[3] Chronic RQ values for freshwater and saltwater fish are based on the 60-d average EEC / NOAEC values of 0.66 mg a.i./L (fathead minnow) and 1.2 mg a.i./L (sheepshead minnow), respectively (see **Table 22**)

Maximum acute RQ values for freshwater invertebrates are three orders of magnitude below the acute risk to listed species LOC while that for saltwater invertebrates marginally exceeds (RQ=0.08) the acute risk to listed species LOC of 0.05 (**Table 29**). Maximum chronic RQ values do not exceed the chronic risk LOC (1.0) for either freshwater or saltwater invertebrates.

Table 29. Maximum acute and chronic risk quotients for freshwater and saltwater Invertebrates based on total residues of interest

Use Category	Crop Scenario	Peak EEC (mg/L)	21-day EEC (mg/L)	Acute RQ [2]		Chronic RQ [3]	
				FW	SW	FW	SW
Cotton	NC Cotton	0.053	0.0529	<0.0001	**0.08**[4]	0.001	0.5

[1] For screening purposes, these EECs are based on total residues of interest (parent + X-474 + X-540).
[2] Acute RQ values for freshwater and saltwater invertebrates are based on the peak EEC / LC_{50} values of >400 mg a.i./L (*Daphnia magna*) and 0.64 mg a.i./L (mysid shrimp), respectively (see **Table 22**)
[3] Chronic RQ values for freshwater and saltwater invertebrates are based on the 21-d average EEC / NOAEC values of 50.5 mg a.i./L (*D. magna*) and 0.11 mg a.i./L (mysid shrimp), respectively (see **Table 22.**)
[4] **Bolded** value exceeds acute risk to listed species LOC of 0.05.

Since the maximum acute RQ for saltwater invertebrates exceeds the acute risk to listed species LOC based on total residues of interest, acute RQ values were re-calculated with refined EECs that include only the toxicological residues of concern (parent + X-540) for those exposure scenarios with RQs that exceed the LOC. These refined RQ values are shown in **Table 30** and are well below LOCs for non-listed and listed species.

Table 30. Acute risk quotients for saltwater invertebrates using refined EECs based on total toxic residues of concern

Crop (State)	Crop(s)	Scenario	EEC Total (ug ai/L)[1]	Acute RQ [2,]
Beans (MI)	Beans (dry & Lima, snab)	MIbeansSTD	5.5	0.009
Citrus (FL)	Citrus	FLcitrusSTD	4.9	0.008
Cotton (NC)	Cotton	NCcottonSTD	4.6	0.007
Cotton (MS)	Cotton	MScottonSTD	4.6	0.007
Vegetables: Brassica (cole) Leafy	Broccoli, Brussels sprouts, Cabbage, Cauliflower, Kale	FLcabbageSTD	1.1	0.002
Vegetables: Bulb (GA)	Onion (dry/green) & Pearl	GAOnion_WirrigSTD	3.1	0.005
Vegetables: Leafy except Brassica	Lettuce/Celery/ Spinach	CAlettuceSTD	1.7	0.003
Vegetables: Root & tuber	Potatoes, Turnip& Rutabaga	MEpotatoSTD	2.5	0.004
Vegetables: Root & tuber	Sweet Potatoes	NCsweetpotatoSTD	4.2	0.007

[1] EECs are based on total toxic residues of concern (parent + X-540; see **Table 17)**.
[2]Acute RQ values for saltwater invertebrates are based on the peak EEC / LC_{50} values of 0.64 mg a.i./L (mysid shrimp; see **Table 22**).

5.1.1.2. Aquatic Invertebrates: Sediment Exposure

Risk quotients for freshwater and saltwater benthic invertebrates using the crop exposure scenario with the highest acute and chronic EEC in sediment porewater (NC cotton) are provided in **Table 31**. For estimating acute risks to benthic invertebrates, risk quotients were determined using peak porewater EECs (reported in **Table 18**) divided by the lowest acute toxicity endpoint for fresh and saltwater water column invertebrates, since acute toxicity data were not available from sediment toxicity studies. For estimating chronic risks to benthic invertebrates, risk quotients were determined by dividing the highest 21-d average EEC in pore water by the lowest pore water NOAEC obtained for the midge (freshwater) and water column exposure NOAEC for mysid shrimp. As the pore water EECs were nearly identical to the water column EECs, RQ values based on water column toxicity data (acute FW & SW, chronic SW) are identical to those described earlier in **Table 29**. For fresh water benthic invertebrates, a slight exceedance (RQ=0.08) of the acute risk to listed species LOC and the chronic risk (RQ=1.4) LOC is indicated.

Table 31. Maximum acute and chronic risk quotients for freshwater and saltwater benthic invertebrates based on total residues of interest

Use Category	Crop Scenario	Peak Pore Water EEC [1] (mg/L)	21-day Pore Water EEC[1] (mg/L)	Acute RQ [2, 3]		Chronic RQ [3, 4]	
				FW	SW	FW	SW
Cotton	NC Cotton	0.051	0.050	<0.0001	**0.08**	**1.4**	0.5

[1] For screening purposes, these EECs are based on total residues of interest (parent + X-474 + X-540).
[2] Acute RQ values for benthic freshwater and saltwater invertebrates are based on the peak pore water EEC / EC_{50} values of >400 mg ai/L (*Daphnia magna*) and an LC_{50} value of 0.64 mg ai/L (mysid shrimp), respectively (see **Table 22**)
[3] Chronic RQ values for freshwater and saltwater benthic invertebrates are based on the 21-d average pore water EEC / 28-d NOAEC values of 0.037 mg ai/L-pore water (*Chironomus riparius)* and 0.11 mg ai/L (mysid shrimp), respectively (see **Table 22**)
[3] **Bolded** value exceeds acute risk to listed species LOC of 0.05
[4] **Bolded** value exceeds chronic risk to listed species LOC of 1.0

Since the maximum acute RQ for saltwater benthic invertebrates using the total residues of interest exceeds the acute risk to listed species LOC and the maximum chronic RQ for freshwater benthic invertebrates the chronic risk LOC, acute and chronic RQ values were for those scenarios exceeding the LOCs were re-calculated using just the residues of toxicological concern (parent and X-540). Those RQ values that exceeded the acute risk to listed species LOCs and chronic risk LOCs are provided in **Table 32.** These refined RQ values are well below acute and chronic risk LOCs for non-listed and listed species.

Table 32. Risk quotients for benthic Invertebrates using refined EECs based on total toxic residues of concern

Crop (State)	Crop(s)	Scenario	Peak Pore Water EEC (mg ai/L)	SW Acute RQ [1]	21-d Avg. Pore Water EEC (mg ai/L)	FW Chronic RQ [2]
Beans (MI)	Beans (dry & Lima, snab)	MIbeansSTD	4.06	0.006	4.06	0.11
Citrus (FL)	Citrus	FLcitrusSTD	2.67	0.004	2.67	0.07
Cotton (NC)	Cotton	NCcottonSTD	3.37	0.005	3.32	0.09
Cotton (MS)	Cotton	MScottonSTD	3.40	0.005	3.35	0.09
Vegetables: Brassica (cole) Leafy	Broccoli, Brussels sprouts, Cabbage, Cauliflower, Kale	FLcabbageSTD	0.65	0.001	0.65	0.02
Vegetables: Bulb (GA)	Onion (dry/green) & Pearl	GAOnion_WirrigSTD	2.02	0.003	2.02	0.05
Vegetables: Leafy except Brassica	Lettuce/Celery/ Spinach	CAlettuceSTD	1.33	0.002	1.33	0.04
Vegetables: Root & tuber	Potatoes, Turnip& Rutabaga	MEpotatoSTD	2.48	0.004	2.47	0.07
Vegetables: Root & tuber	Sweet Potatoes	NCsweetpotatoSTD	3.21	0.005	3.21	0.09

Crop (State)	Crop(s)	Scenario	Peak Pore Water EEC (mg ai/L)	SW Acute RQ [1]	21-d Avg. Pore Water EEC (mg ai/L)	FW Chronic RQ [2]
[1] Acute RQ values for benthic saltwater invertebrates are based on the peak pore water EEC / LC_{50} value 0.64 mg ai/L (mysid shrimp; see **Table 22**) [2] Chronic RQ values for freshwater benthic invertebrates are based on the 21-d average pore water EEC / 28-d NOAEC values of 0.037 mg ai/L-pore water (*Chironomus riparius;* see **Table 22**)						

5.1.2 Risks to Aquatic Plants

Risk quotients calculated for vascular and non-vascular aquatic plants using the crop exposure scenario with the highest acute and chronic EECs in surface water (NC cotton) are provided **Table 33.** None of the risk quotients exceed the LOC for listed or non-listed aquatic plant species.

Table 33. Maximum acute and chronic risk quotients for non-vascular and vascular aquatic plants

Use Category	Crop Scenario	Peak EEC (mg/L) [1]	Non-Vascular Plant RQ [2]		Vascular Plant RQ [3]	
			Non-Listed	Listed	Non-Listed	Listed
Cotton	NC Cotton	0.0530	<0.0007	0.02	<0.0005	0.0005
[1] For screening purposes, these EECs are based on total residues of interest (parent + X-474 + X-540). [2] RQ values for non-listed and listed non-vascular aquatic plants are based on the peak surface water EEC / EC_{50} value of >95.6 mg ai/L and a 96-h NOAEC of 3.54 mg ai/L, respectively (freshwater diatom, *Navicula pelliculosa*; see **Table 22**) [3] RQ values for non-listed and listed vascular aquatic plants are based on the peak surface water EEC / 7-d EC_{50} value of >99 mg ai/L and a 7-d NOAEC of 99 mg ai/L, respectively (Duckweed *(Lemna gibba;* see **Table 22**)						

5.1.3 Risks to Terrestrial Animals

Potential risks to mammals and birds are derived using T-REX (version 1.5) with biological inputs including: 1) acute and chronic toxicity data for the rat and mallard, 2) weights of three mammalian and avian size classes, and 3) various dietary categories being consumed. Chemical-specific inputs include: 1) application rate, 2) application interval, 3) frequency of applications, and a chemical-specific foliar dissipation rate of 12.3 days.

For sulfoxaflor, the proposed use pattern encompasses four different modeling scenarios for T-REX:

- **2 x 0.133 lb ai/A @ 7 d interval** (citrus, fruits-pome, fruits-stone, ornamentals, tree nuts, turf grass)
- **3 x 0.090 lb ai/A @ 7 d interval** (beans, berries, soybeans, veg.-brassica, veg.-bulb, veg.-leafy, veg.-root/tuber, veg.-fruiting, veg.-cucurbit, watercress)
- **3 x 0.090 lb ai/A @ 5 d interval** (cotton), and
- **2 x 0.043 lb ai/A @ 14-d intervals** (canola and grains)

Of these exposure scenarios, the first (2 x 0.133 lb ai/A @ 7 d interval) yields the highest residues on terrestrial forage items. Therefore, it is used here as an initial screen for evaluating whether the proposed uses of sulfoxaflor have potential risks to avian and mammalian wildlife.

5.1.3.1. Acute Risk to Mammals

Acute mammalian RQ values are calculated using the rat acute oral toxicity data (LD_{50} =1000 mg/kg b.w.) adjusted for differences in body weight for a small (15g), medium (35g) and large (1000g) mammal by T-REX (adjusted LD_{50} =2198, 1778, and 769 mg/kg b.w., respectively) and the modeled acute dose-based EECs for various use scenarios and diet categories. Results from the application scenario providing the highest residues on forage items (Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass) are provided in **Table 34.** These results are based on the 90th percentile foliar dissipation half life of 12.3 days for sulfoxaflor. Maximum acute mammalian RQ values are all below 0.1 which indicates a low acute risk potential to listed and non-listed mammals consuming the modeled forage items.

Table 34. Maximum acute dose-based risk quotients for mammals

Size Class (g)	Adjusted LD_{50} (mg/kg-bw)	EECs (mg a.i./kg bw) and RQs[1,2]											
		Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/ Seeds		Arthropods		Granivore	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
2 x 0.133 lb ai/A, 7 d Interval (Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass													
15	2198	51.0	0.02	23.2	0.01	28.7	0.01	3.2	0.00	20.0	<0.01	0.71	<0.01
35	1778	35.2	0.02	16.1	0.01	19.8	0.01	2.2	0.00	13.8	<0.01	0.49	<0.01
1000	769	8.2	0.01	3.7	< 0.00	4.6	0.01	0.5	0.00	3.2	<0.01	0.11	<0.01

[1] EECs calculated using T-REX based on sulfoxaflor-specific foliar dissipation half life of 12.3 days.
[2] Acute RQ values calculated as EEC/size class-adjusted LD50 based on unadjusted LD50 of 1000 mg a.i./kg bw for the rat (MRID 47832144).

5.1.3.2. Chronic Risks to Mammals

Potential chronic risks to mammals are derived using a dietary-based NOAEL of 100 ppm from a 2-generation reproduction study with the rat (MRID 47832142) and EECs for the crop exposure scenario yielding the maximum residues on forage items (2 x 0.133 lb ai/A). The chronic dietary-based RQ values range from **0.03** (Fruits, pods, seeds, large insects) to **0.5** (short grass). Since these chronic RQ values are all below the chronic risk LOC of 1.0, the potential for chronic risks to mammals is based on a dietary approach is considered low (**Table 35**).

Table 35. Maximum chronic diet-based risk quotients for mammals

NOAEC (ppm in diet)	EECs (ppm diet) and RQs[1,2]									
	Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/Seeds /Large Insects		Arthropods	
	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
	2 x 0.133 lb ai/A, 7 d Interval (Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass)									
100	53.4	0.53	24.5	0.24	30.1	0.30	3.3	0.03	20.9	0.21

[1] EECs calculated using T-REX based on sulfoxaflor-specific foliar dissipation half life of 12.3 days.
[2] Chronic RQ values calculated based on the dietary EEC / NOAEC of 100 ppm in the diet (MRID 47832142

Potential chronic risks to mammals are also evaluated using a dose-based approach which relies on a NOAEL of 6.07 mg a.i./kg bw/d from the same 2-generation toxicity rat study (MRID 47832142). This dose-based NOAEL is adjusted in the T-REX model to account for different size classes of mammals. Specifically, body-weight adjusted NOAELs of 13.3, 10.8, and 4.7 mg a.i./kg bw/d were calculated 15g, 35g and 1000g mammals, respectively. These adjusted values are used to interpret the dose-based EECs calculated for the same mammalian size classes. The overall range in chronic RQ values is from **0.01 to 3.8**, and the potential for chronic risks to mammals is identified for all crop scenarios for at least one dietary category (**Table 36**).

Table 36. Chronic dose-based RQ values for mammals

Size Class (g)	Adjusted NOAEL (mg a.i./kg bw/d)	EECs (mg a.i./kg bw/d) and RQs[1,2]											
		Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/ Seeds		Arthropods		Granivore	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
2 x 0.133 lb ai/A, 7 d Interval (Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass													
15	13.3	50.9	**3.8**	23.4	**1.8**	28.7	**2.1**	3.2	0.24	20.0	**1.5**	0.71	0.05
35	10.8	35.2	**3.3**	16.1	**1.5**	19.8	**1.8**	2.2	0.20	13.8	**1.3**	0.49	0.05
1000	4.7	8.2	**1.7**	3.7	0.80	4.6	0.98	0.51	0.11	3.2	0.68	0.11	0.02
3 x 0.090 lb ai/A, 7 d Interval (Beans, Berries, Soybeans, Veg.-Brassica, Veg.-Bulb, Veg.-Leafy, Veg.-Root/Tuber, Veg.-Fruiting, Veg.-Cucurbit, Watercress)													
15	13.3	47.9	**3.6**	21.9	**1.6**	26.9	**2.0**	3.0	0.22	18.7	**1.4**	0.66	0.05
35	10.8	33.1	**3.1**	15.2	**1.4**	18.6	**1.7**	2.1	0.19	13.0	**1.2**	0.46	0.04
1000	4.7	7.7	**1.6**	3.5	0.75	4.31	0.92	0.48	0.10	3.0	0.64	0.11	0.02
3 x 0.090 lb ai/A, 5 d Interval (Cotton)													
15	13.3	53.4	**4.0**	24.5	**1.8**	30.0	**2.3**	3.3	0.25	20.9	**1.6**	0.74	0.06
35	10.8	36.9	**3.4**	16.9	**1.6**	20.8	**1.9**	2.3	0.21	14.5	**1.3**	0.51	0.05
1000	4.7	8.6	**1.8**	3.9	0.84	4.8	**1.0**	0.53	0.11	3.4	0.72	0.12	0.03
2 x 0.043 lb ai/A, 14-d Intervals (Canola, Grains)													
15	13.3	14.3	**1.1**	6.6	0.49	8.0	0.60	0.89	0.07	5.6	0.42	0.20	0.01
35	10.8	9.9	0.92	4.5	0.42	5.6	0.52	0.62	0.06	3.9	0.36	0.14	0.01
1000	4.7	2.3	0.49	1.1	0.23	1.3	0.28	0.14	0.03	0.90	0.19	0.03	0.01

Size Class (g)	Adjusted NOAEL (mg a.i./kg bw/d)	EECs (mg a.i./kg bw/d) and RQs[1,2]											
		Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/ Seeds		Arthropods		Granivore	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
[1] EECs calculated using T-REX based on sulfoxaflor-specific foliar dissipation half life of 12.3 days.													
[2] Chronic dose-based RQ values calculated as dietary EEC / size class-adjusted NOAEC based on an unadjusted NOAEC of 6.7 mg/kg bw/d (MRID 47832142)													
RQ values shown in **bold** exceed the chronic risk LOC of 1.0													

5.1.3.3. Acute Risk to Birds

For sulfoxaflor, avian dose-based acute RQs are based on the zebra finch acute oral toxicity data (LD_{50} > 80 mg a.i./kg bw; MRID 47832072) which reflects the concentration above which dose-dependent effects of regurgitation were observed. Thus, a value of 80 mg a.i./kg bw is used as a conservative screen for acute risks to birds. Acute dose-based RQ values are based on LD_{50} values adjusted differences in body weight for birds (20, 100, 1000g) (adjusted LD_{50} =86.4, 110 and 155 mg a.i./kg bw, respectively) and modeled acute dose-based EECs for various use scenarios and diet categories and a sulfoxaflor-specific foliar DT_{50} of 12.3 days.

Avian acute RQs for sulfoxaflor are shown in **Table 37**. The overall range in acute RQ values is from <**0.01 to 0.70**, and the potential for acute risks to birds (including reptiles and terrestrial-phase amphibians) is identified for all crop scenarios for at least one dietary category

Table 37. Acute dose-based risk quotients for birds

Size Class (g)	Adjusted LD_{50} (mg a.i./kg-bw)	EECs (mg a.i./kg-bw) and RQs*											
		Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/Seeds		Arthropods		Granivore	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
2 x 0.133 lb ai/A, 7 d Interval (Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass													
20	86.4	60.9	**<0.70**	27.9	**<0.32**	34.2	**<0.40**	3.8	<0.04	23.8	**<0.28**	0.85	<0.01
100	110	34.7	**<0.32**	15.9	**<0.14**	19.5	**<0.18**	2.2	<0.02	13.6	**<0.12**	0.48	<0.00
1000	155	15.5	**<0.10**	7.1	<0.05	8.7	<0.06	0.97	<0.01	6.1	<0.04	0.22	<0.00
3 x 0.090 lb ai/A, 7 d Interval (Beans, Berries, Soybeans, Veg.-Brassica, Veg.-Bulb, Veg.-Leafy, Veg.-Root/Tuber, Veg.-Fruiting, Veg.-Cucurbit, Watercress)													
20	86.4	57.2	**<0.66**	26.2	**<0.30**	32.2	**<0.37**	3.6	<0.04	22.4	**<0.26**	0.79	<0.01
100	110	32.6	**<0.30**	14.9	**<0.14**	18.3	**<0.17**	2.0	<0.02	12.8	**<0.12**	0.45	<0.01
1000	155	14.6	<0.09	6.7	<0.04	8.2	<0.05	0.91	<0.01	5.7	<0.04	0.20	<0.01
3 x 0.090 lb ai/A, 5 d Interval (Cotton)													
20	86.4	63.8	**<0.74**	29.2	**<0.34**	35.9	**<0.42**	4.0	<0.05	25.0	**<0.29**	0.89	<0.01
100	110	36.4	**<0.33**	16.7	**<0.15**	20.5	**<0.19**	2.3	<0.02	14.2	**<0.13**	0.51	<0.01
1000	155	16.3	**<0.10**	7.5	<0.05	9.2	<0.06	1.0	<0.01	6.4	<0.04	0.23	<0.01
2 x 0.043 lb ai/A, 14-d Intervals (Canola, Grains)													

Size Class (g)	Adjusted LD_{50} (mg a.i./kg-bw)	EECs (mg a.i./kg-bw) and RQs*											
		Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/Seeds		Arthropods		Granivore	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
20	86.4	17.1	**<0.20**	7.8	<0.09	9.6	**<0.11**	1.1	<0.01	6.7	<0.08	0.24	<0.01
100	110	9.7	<0.09	4.5	<0.04	5.5	<0.05	0.61	<0.01	3.8	<0.03	0.14	<0.01
1000	155	4.4	<0.03	2.0	<0.01	2.5	<0.02	0.27	<0.00	1.7	<0.01	0.06	<0.01

[1] EECs calculated using T-REX based on sulfoxaflor-specific foliar dissipation half life of 12.3 days.
[2] Acute RQ values calculated as EEC/size class-adjusted LD50 based on unadjusted LD50 of 80 mg a.i./kg bw for the zebra finch (MRID 47832072)
RQ values shown in **bold** exceed the acute risk to listed species LOC of 0.1

Avian subacute dietary-based acute risk quotients for the crop scenario resulting in the maximum residues on forage items are provided in **Table 38**. These RQ values are based on the dietary LC_{50} of 5,620 ppm diet for the mallard duck (MRID 47832104) and a sulfoxaflor-specific foliar dissipation half life of 12.3 days. No subacute acute risk is identified with the dietary-based approach, as RQ values are all well below the acute risk to listed species LOC of 0.1.

Table 38. Maximum acute diet-based risk quotients for birds

LC_{50} (ppm diet)	EECs (ppm in diet) and RQs[1,2]									
	Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/Seeds		Arthropods	
	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
	2 x 0.133 lb ai/A, 7 d Interval (Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass									
5620	53.44	0.01	24.49	<0.01	30.06	0.01	3.34	<0.01	20.93	<0.01

[1] EECs calculated using T-REX based on sulfoxaflor-specific foliar dissipation half life of 12.3 days.
[2] Acute RQ values calculated as EEC/subacute LC50 of 5,620 ppm diet for mallard (MRID 47832104)

Potential chronic effects to terrestrial birds (including reptiles and terrestrial-phase amphibians) are derived by considering highest dietary-based EECs modeled in T-REX for a bird consuming a variety of dietary items. Chronic effects are estimated using the lowest available chronic dietary toxicity data for birds (NOAEC= 200 mg/kg-diet for mallard duck) and a sulfoxaflor-specific foliar dissipation half life of 12.3 days. Chronic dietary-based RQs range from **0.02 to 0.27** (**Table 39)**, thus indicating a low potential for chronic risks to birds.

Table 39. Maximum chronic diet-based risk quotients for birds

NOAEC (ppm)	EECs and RQs[1, 2]									
	Short Grass		Tall Grass		Broadleaf Plants		Fruits/Pods/Seeds		Arthropods	
	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
	2 x 0.133 lb ai/A, 7 d Interval (Citrus, Fruits-Pome, Fruits-Stone, Ornamentals, Tree nuts, Turf grass									
200	53.44	0.27	24.49	0.12	30.06	0.15	3.34	0.02	20.93	0.10

[1] EECs calculated using T-REX based on sulfoxaflor-specific foliar dissipation half life of 12.3 days.
[2] Chronic RQ values calculated as EEC/dietary NOAEC of 100 ppm diet for the rat (MRID 47832142)

5.1.3.4. Non-target Terrestrial and Semi-Aquatic Plants

For sulfoxaflor, the NOAEC values from seedling emergence and vegetative vigor toxicity tests of terrestrial plants are above the maximum single application rate of 0.133 lb ai/A (MRID 47832425 and 47832427) . Therefore, a low potential for risk to listed and non-listed terrestrial plants is expected based on the proposed use profile for sulfoxaflor.

5.1.3.5. Risk Estimation for Bees

Figure 15 illustrates the proposed decision-making process for assessing risks to honey bees associated with foliar spray applications of pesticides (*e.g.*, via ground and aerial methods) including systemic pesticides such as sulfoxaflor. This decision-making framework was recently presented and reviewed by a FIFRA Scientific Advisory Panel.[17] The overall proposed approach is a tiered process whereby risks are first assessed using simple and conservative exposure screening models to generate estimated environmental concentrations (EECs) (**Boxes 3a**, **3b** and **3c** of **Figure 15**) coupled with toxicity estimates derived from laboratory studies (Tier I) to calculate risk quotients (RQs) (**Boxes 4a**, **4b** and **4c**). Results from the Tier I risk assessment process are expected to be reasonably conservative such that the likelihood of a false negative is low (*i.e.*, the chance that no risk is indicated but risks actually occur), while at the same time ensuring that the likelihood of a false positive (*i.e.*, the chance that risk is indicated when none actually exists) is not unacceptably high. For example, the initial exposure estimates used in Tier I are generally not chemical-specific, but rather reflect upper-bound estimates that would encompass exposures across all relevant pesticide uses. If risks are identified in Tier I (*i.e.*, where risk estimates exceed levels of concern[18]; **Box 5**), additional data may be used to refine the results, such as using estimates of exposure derived from available magnitude of residue or other commonly submitted studies (**Box 6)**.

If risks are still identified after refinement with available data (**Box 7**), then appropriate risk mitigation options would be identified and further evaluated for their impact on risk estimates (**Box 8**). Alternatively (or in addition), a higher tier assessment may be necessary (Tier II) and studies providing refined estimates of exposure (*e.g.*, field studies quantifying residues in pollen and nectar; **Box 9a**) and effects at the colony level (*e.g.*, semi-field tunnel studies or field-level feeding studies; **Box 9b**) may be requested. Measured residues in pollen and nectar (**Box 9a**) from these studies may be used to refine risk estimates from Tier I (**Box 6**) and/or for qualitatively evaluating risk at the colony level associated with pesticide applications (**Box 10**). They may also be used to identify more targeted risk mitigation options than those that could be identified based on Tier I risk estimates.

Although not specifically depicted in **Figure 15** for foliar applications, data from the toxicity of residues on foliage study are used qualitatively to characterize the length of time that residues

[17] http://www.epa.gov/scipoly/sap/meetings/2012/091112meeting.html).
[18] As described in USEPA (2012), an acute risk level of concern of 0.4 is proposed for the honey bee.

remain toxic to bees. The results of the guideline study may result in precautionary label statements similar to those discussed in the EPA Label Review Manual (USEPA 2012) or in guidance documents intended to reduce the potential effects of pesticides on bees (*e.g.*, Riedl *et al*. 2006).

If available risk mitigation options (**Box 11**) do not provide for an acceptable reduction in risk, proceeding to Tier III (**Box 12**) may be necessary to resolve specific uncertainties identified from Tiers I and II for the proposed uses of the pesticide. For example, effects on the ability of colonies to successfully emerge in the spring (*e.g.*, produce sufficient brood and adult bees after over-wintering) may be a concern for some pesticides/uses which are not typically addressed in earlier tiers.

The risk assessment process depicted in **Figure 15** is intended to be iterative and to rely on multiple lines of evidence to further refine and characterize potential risk. At a screening level, risk to individual bees is quantified through the use of RQ values. Where RQ values exceed the LOC, more refined estimates of exposure may be used to re-evaluate RQ values for individual bees based on laboratory toxicity estimates. Where RQs still exceed LOCs, higher tier semi-field and full-field studies may be required to determine whether effects observed under highly controlled conditions extend to the whole colony under increasingly realistic exposure conditions.

As depicted in **Figure 15,** if the multiple lines of evidence indicate that unacceptable effects on survival, growth or reproduction of the colony are not likely, then a presumption of minimal risk can be supported. Alternatively, there may be situations where colony-level effects may be likely, given the proposed use or known mode of action of a compound. In this case, a presumption of minimal risk cannot be supported, and risk assessors should attempt to characterize the nature and possible magnitude and duration of the effect. This characterization should include a discussion of uncertainties which limit the extent to which the possible magnitude and duration can be estimated. Also, the risk characterization should include any potential mitigation options for minimizing risk to bees from the proposed use of a pesticide.

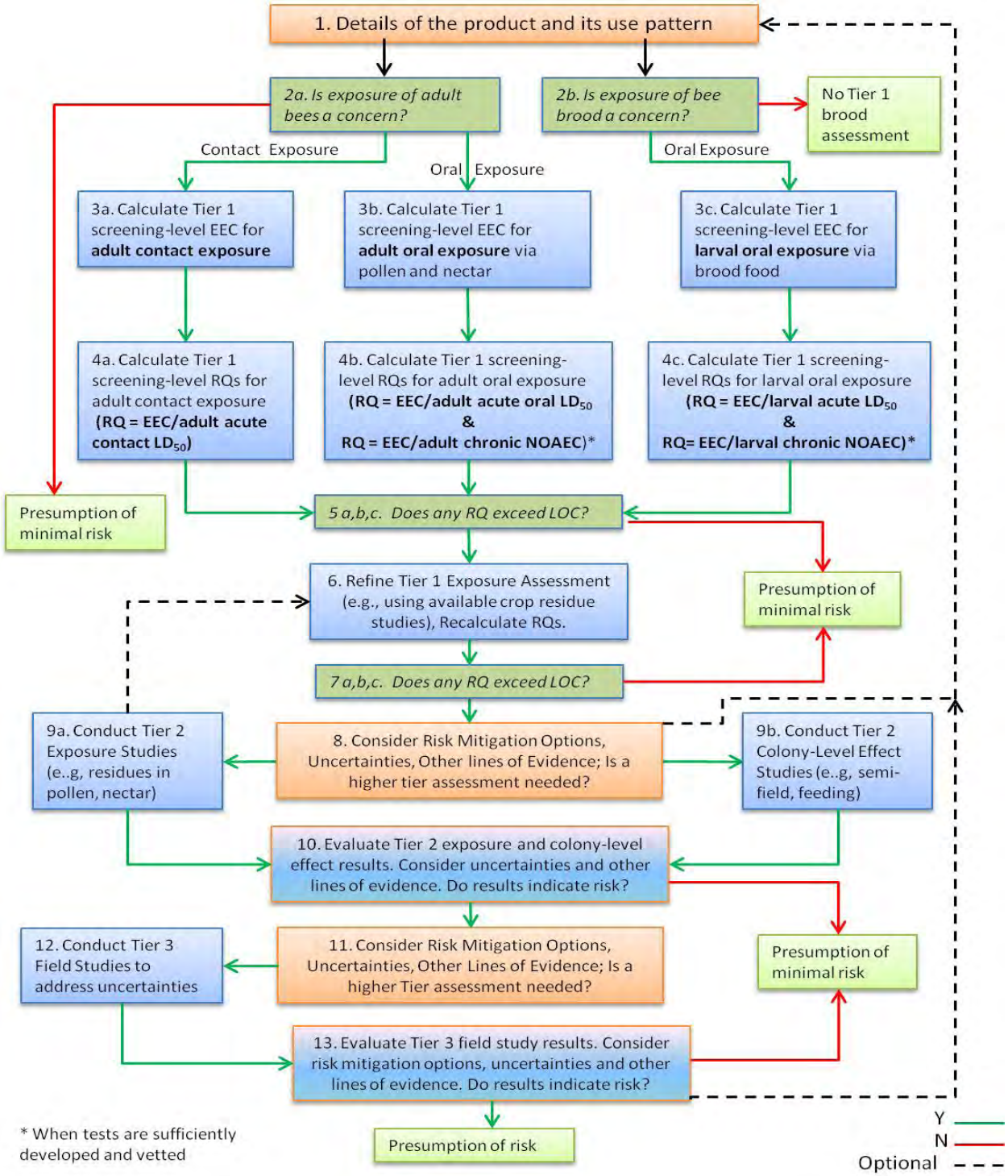


Figure 15. Proposed Tiered Approach for Assessing Risk to Honey Bees from Foliar Spray Applications

a) Tier 1 Risk Estimation for Honey Bees

For the initial Tier 1 screen, two exposure routes are considered: dietary and contact. **Table 40** summarizes the initial residue values expressed in units of μg a.i./bee per 1 lb a.i./A. As discussed below, these values are adjusted to account for the application rate of the chemical. For generating RQs, dietary based exposure values are compared to oral toxicity data for larvae and adult worker bees while contact exposure values are compared to acute contact toxicity data for adult worker bees.

As indicated in **Table 40,** the initial screening-level RQs exceed the proposed LOC of 0.4 for adults (oral and contact) exposures. Therefore, additional refinement of the Tier 1 exposure estimates is warranted.

Table 40. Tier I exposure values of honey bees to pesticides applied via foliar applications

Life Stage	Exposure Type	Dose (μg a.i./bee per 1 lb a.i./A)[(1)]	Sulfoxaflor Dose for Max Application Rate (μg a.i./bee per 0.133 lb a.i./A)	Acute RQ)[(2)(3)]	Chronic RQ)[(3)]
Adult	Diet (nectar + pollen)	32	4.3	**83**	n.a.
Adult	Direct contact	2.7	0.72	**2.8**	n.a.

(1) Source: USEPA 2012. Draft Pollinator Risk Assessment Framework
(2) Based on a 48-h acute oral LD_{50} of 0.0515 ug ai/bee for GF-2032 (MRID 47832417) and acute contact LD_{50} of 0.130 ug ai/bee for GF-2032 (MRID 47832419).
(3) **Bolded** value exceeds the acute risk LOC of 0.4

b) Refined Tier 1 Risk Estimation for Honey Bees

Sulfoxaflor Residue Studies

As indicated in **Box 6** of **Figure 15**, refinements of Tier 1 risk estimation for oral exposure can be accomplished by using chemical-specific data on residues in pollen and nectar. For sulfoxaflor, such residue data are available from multiple studies including a field residue study with cotton (MRID 48755606), pumpkin (MRID 48755601) and *Phacelia* (MRID 48446601 and 48445806). Maximum reported residues in various plant and hive matrices are shown in **Table 41.** Details of these studies are provided in **Appendix D.**

Table 41. Maximum reported residues (ppm) of sulfoxaflor in plant and hive materials from various field studies

Application Rate (lb ai/A)	Plant Pollen*	Plant Nectar	Plant Tissue	Forager Nectar*	Forager Pollen	Comb Pollen	Comb Larvae	MRID
Cotton								
1 x 0.045	1.26			0.13	0.22	0.03	<0.01	48755606
2 x 0.045	2.54			0.05	0.83	0.04	0.01	
2 x 0.089	**6.66**			0.07	2.78	1.19	0.03	
2 x 0.134	2.61			**1.01**	2.23	0.04	0.08	

Application Rate (lb ai/A)	Plant Pollen*	Plant Nectar	Plant Tissue	Forager Nectar*	Forager Pollen	Comb Pollen	Comb Larvae	MRID
Phacelia								
1 x 0.021			0.52[b]	0.05	0.29			48446601
1 x 0.043			1.48[b]	0.09	0.81			
Phacelia								
1 x 0.006						0.06[a]		48445806
1 x 0.012						0.04[a]		
1 x 0.021			1.76[b]			0.61[a]		
1 x 0.045						0.23[a]		
1 x 0.088						1.01[a]		
Pumpkin								
1 x 0.022	0.08	0.03	0.20[b]					48755601
1 x 0.089	0.38	0.03	1.27[b]					

[a] Samples taken 7 days after treatment rather than immediately after treatment
[b] Whole plant samples in 48446601, flower samples in 48445806, leaf tissue in 48755601
* Overall maximum reported residue in pollen and nectar used for Tier 1 risk assessment is shown in bold

Honey Bee Pollen and Nectar Consumption Rates

Estimation of honey bee consumption of pollen and nectar depends on the caste and life stage of the bee. Consumption rates for different castes, life stages and tasks of honey bees have been recently reviewed and summarized in USEPA (2012). A summary of these consumption rate estimates is found in **Appendix D**. As indicated in **Table 42,** the highest consumption rates for worker, drone, and queen larvae occur on the last days of their life stage. Therefore, for Tier 1 risk assessment purposes, the latter two days of the worker and drone pollen and nectar consumption rates is used for calculating oral doses of sulfoxaflor. Feedback from the FIFRA SAP on the draft pollinator risk assessment framework indicated that consumption rates should be summed across the entire larval life stage. It is noted here that assessment of doses of sulfoxaflor in royal jelly is not conducted because available data indicate residues in royal jelly are reduced by 100X or greater presumably due to processing of material by nurse bees (Davis and Shuel 1988 and Kamel *et al*. (unpublished)). Estimated consumption rates for adult honey bees are provided in **Table 43**.

Table 42. Estimated consumption rates of pollen, nectar and royal jelly by larval honey bees

Life Stage	Caste	Average age (in days)*	Daily consumption rate (mg/day)			
			Brood food / royal jelly	Nectar**	Pollen***	Total food
Larval	Worker	1	3.75	none	none	3.75
		2	7.50	none	none	7.50
		3	15	none	none	15
		4	none	37	2.7	40
		5	none	77	2.7	80

Life Stage	Caste	Average age (in days)*	Daily consumption rate (mg/day)			
			Brood food / royal jelly	Nectar**	Pollen***	Total food
		Days 4+5	**none**	**114**	**5.4**	**119**
	Drone	5	none	52	unknown	52
		6	none	100	unknown	100
		Days 5+6	**none**	**152**	**Unknown**	**152**
	Queen	1	9.4	none	none	9.4
		2	19	none	none	19
		3	38.0	none	none	38
		4	100.0	none	none	100
		5	203	none	none	203

Source: USEPA 2012 Draft Pollinator Risk Assessment Framework; highlighted row indicates consumption rate estimates used for the refined Tier 1 risk assessment;
NA = not applicable
*From Winston 1987
**From Rortais *et al.* 2005. Assumes that average sugar content of nectar is 30%.
*** From Crailsheim et al. (1992, 1993).

Table 43. Estimated consumption rates of pollen, nectar and royal jelly by adult honey bees

Life Stage	Caste	Daily consumption rate (mg/day)				
		Average Age (in days)	Brood food / royal jelly	Nectar**	Pollen***	Total food
Adult	Worker (cell cleaning and capping)	0-10	none	60	5.2	65
	Worker (brood and queen tending, nurse bees)	6-17	none	140	8.85	149
	Worker (comb building, cleaning and food handling)	11-18	none	60	1.7	62
	Worker (foraging for pollen)	>18	none	43.5	0.041	44
	Worker (foraging for nectar)	>18	none	292	0.041	292
	Worker (maintenance of hive in winter	0-90	none	29	2	31
	Drone	>10	none	235	0.0002	235
	Queen	0+	Unknown	unknown	None	unknown

Source: USEPA 2012 Draft Pollinator Risk Assessment Framework;
NA = not applicable
*From Winston 1987
**From Rortais *et al.* 2005. Assumes that average sugar content of nectar is 30%.
*** From Crailsheim et al. (1992, 1993).

Honey Bee Oral Dose Estimation

By combining the maximum reported residues of sulfoxaflor in pollen and nectar with the estimated consumption rates shown in **Table 42** and **Table 43**, a total oral dose is estimated. This oral dose is then divided by the applicable acute oral LD_{50} (0.0515 µg ai/bee for adult workers and >0.2 µg ai/bee for larvae, respectively) to derive the acute RQ values (**Table 44**). Chronic toxicity data of sulfoxaflor to honey bees are not available nor have standardized test protocols for chronic toxicity testing of individual bees been developed. As indicated in **Table 44**, RQs range from **<0.8 to 5.7** and exceed the LOC for acute risk (0.4). This indicates that risk to honey bee colonies cannot be precluded and analysis of effects at the whole hive level is warranted (Tier 2). Unlike Tier 1, where risks are expressed quantitatively in the form of RQ values, risk in Tier 2 is described qualitatively and is characterized in **Section 5.2, Risk Description.**

Table 44. Refined Tier 1 oral risk quotients for honey bees using maximum reported concentrations in pollen and nectar

Life Stage	Cast/Task	Average Age (d)	Total food Consumption (mg/d)	Estimated Oral Dose (ug ai/bee/d) [1]	Acute RQ [2, 3]
Larvae	Worker	days 4+5	119	0.151	**<0.8**
	Drone	Days 5+6	152	0.153	**<0.8**
Adult	Worker (cell cleaning and capping)	0-10	65	0.095	**1.8**
	Worker (brood and queen tending, nurse bees)	6-17	149	0.200	**3.9**
	Worker (comb building, cleaning and food handling)	11-18	62	0.072	**1.4**
	Worker (foraging for pollen)	>18	43.5	0.044	**0.9**
	Worker (foraging for nectar)	>18	292	0.294	**5.7**
	Worker (maintenance of hive in winter	0-90	31	0.042	**0.8**
	Drone	>10	235	0.236	**4.6**
	Queen	0+	unknown	unknown	unknown

[1] Oral dose determined using maximum concentrations of sulfoxaflor in pollen (6.6 mg/kg) and nectar (1.0 mg/kg) reported in **Table 41** multiplied by the estimated cast-specific consumption rate.
[2] Acute RQs determined as the ratio of oral dose to the acute LD_{50} for adult (0.0515 µg ai/bee) and larval (>0.2 µg ai/bee) honey bees
[3] RQ values in **bold** exceed the proposed acute risk LOC of 0.4.

Based on the estimate median consumption rates of pollen and nectar shown in **Table 42** and **Table 43**, it is clear that the oral exposure of adult and larval honey bees is dominated by the

consumption of nectar, with more than 90% of the total consumed food source represented by nectar. Given the importance of nectar as a source of food and potential contaminant exposure, the concentration in nectar necessary to meet or exceed the proposed acute risk LOC of 0.4 was determined. Based on the acute LD_{50} of 0.0515 µg a.i./bee and a consumption rate of 292 mg/d for adult nectar foragers, a concentration of **≥ 0.07 ppm** in nectar would result in an acute oral RQ that meets or exceeds the proposed LOC of 0.4. The adult nectar forager caste was chosen because it has the highest estimated nectar consumption rate among the various castes assessed. A comparison of each of the 88 reported residues of sulfoxaflor in cotton nectar reveals that only 4 values (5%) exceeded the 0.07 ppm LOC-based threshold (**Figure 16**). Three of these values are within a factor of two, but one value (1.0 ppm, day 8, 2 x 0.134 lb a.i./A, hive 1) is about 14X above the residue equivalent to the LOC. The vast majority of sulfoxaflor residues in nectar (88%) are less than half the 0.07 ppm LOC-based threshold in nectar. While the concentration of sulfoxaflor in pollen would add to the total dose estimated for nectar foragers, bees, the contribution is very minor and does not affect this interpretation of the results.

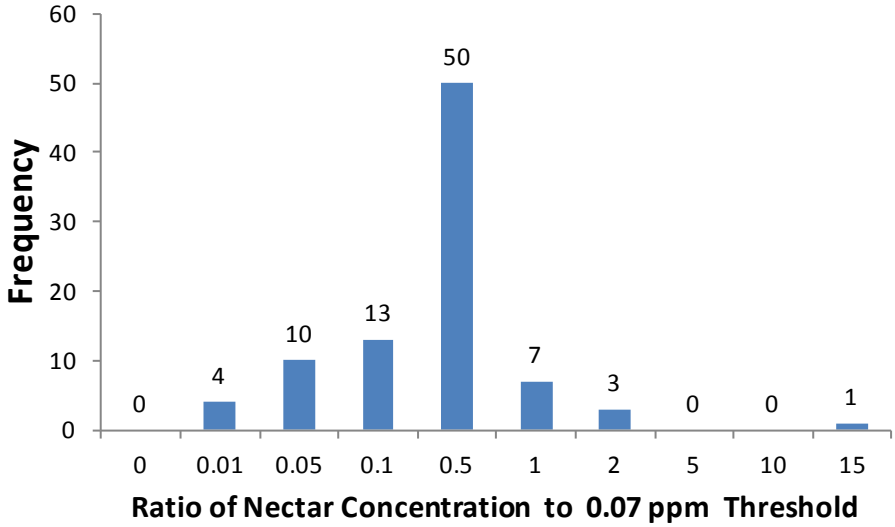


Figure 16. Ratio of sulfoxaflor concentration in cotton nectar to residue associated with the proposed acute LOC of 0.4

5.2 Risk Description - Interpretation of Direct Effects

In risk description, the results from the risk estimation are interpreted and synthesized into overall risk conclusions. This description considers other lines of evidence (*e.g.*, monitoring data, field data, refined exposure and effects modeling) for characterizing ecological risk. In addition, the risk description also contains a discussion of relevant sources of uncertainty in the risk assessment and sensitivity of the risk assessment findings to important methodological assumptions. The risk description also addresses other concerns including risks to threatened and endangered species, a discussion of uncertainty, and the sensitivity of risk conclusions to assumptions made in the assessment.

5.2.1 Risks to Aquatic Animals

A summary of the maximum sulfoxaflor acute and chronic RQ values derived for aquatic animals is shown in **Table 45**. None of these RQ values exceed the applicable acute or chronic risk LOC. Specifically, the acute RQ values are one to two orders of magnitude below the acute risk to listed species LOC of 0.05. The chronic RQ values are one to three orders of magnitude below the LOC, with the exception of saltwater invertebrates, which are within a factor of two of the LOC of 1.0. As discussed in Section 4, chronic RQ for saltwater invertebrates (benthic and water column-dwelling) is based on a NOAEC value for mysid shrimp (0.11 mg a.i./L) that reflects just a 4.5% increase in time to first brood relative to controls at the LOAEC of 0.25 mg a.i./L. No other adverse effects were reported at this concentration for mysid shrimp. Thus, there is some uncertainty regarding the biological significance of this endpoint and consequently, in the RQ values, which are just a factor of two below the chronic LOC.

Because sulfoxaflor is a new chemical, no information is available from monitoring data or ecological incident reports. Based on the results of risk estimation, the potential risk to aquatic animals from the proposed uses of sulfoxaflor is presumed low.

Table 45. Summary of aquatic animal risk profile for sulfoxaflor

Exposure	FW Fish RQ	SW Fish RQ	FW Invert. RQ (water column)	SW Invert. RQ (water column)	FW Invert. RQ (benthic)	SW Invert. RQ (benthic)
Acute	<0.0001	0.0002	<0.0001	0.009	<0.0001	0.006
Chronic	0.08	0.04	0.001	0.5	0.11	0.5
RQ values based on the maximum aquatic EECs derived from the NC Cotton exposure scenario; see Risk Estimation **Section 5.1** for derivation of these RQ values						

5.2.2 Risks to Aquatic Plants

Risk quotient values calculated using the maximum peek aquatic EEC and the lowest toxicity endpoint for aquatic vascular and non-vascular plants are two to three orders of magnitude below levels of concern (**Table 33).** This finding, combined with knowledge of the mode of action of

sulfoxaflor (new class of nicotinic acetylcholine receptor agonist), support a conclusion of low potential risk to aquatic plants.

5.2.3 Risks to Terrestrial Organisms

5.2.3.1. Acute and Chronic Risk to Birds and Mammals

A summary of the overall acute and chronic risk profile for sulfoxaflor based on the exposure scenario producing the highest terrestrial EECs and the most sensitive species within each taxonomic group is shown in **Table 46.**

Table 46. Summary of the avian and mammalian risk profile for sulfoxaflor

Exposure	Avian Dose RQ	Avian Dietary RQ	Mammalian Dose RQ	Mammalian Dietary RQ
Acute	**<0.74**	0.01	0.02	n/a
Chronic	n/a	0.27	**3.8**	0.53

RQ values based on the maximum terrestrial EECs derived from 2 x 0.133 lb ai/A, 7 d interval exposure scenario; see Risk Estimation **Section 5.1** for derivation of these RQ values
* Refined RQ estimate using a foliar dissipation half life of 12.3 days
Bolded value exceeds chronic risk LOC

For birds (also used as a surrogate for terrestrial-phase amphibians and reptiles), a potential for acute risks is identified using the acute dose-based RQ approach. Specifically, a maximum RQ of <0.74 was determined using a sulfoxaflor-specific foliar dissipation half life of 12.3 days. Although a risk potential is indicated by this acute RQ, it is considered uncertain because the acute toxicity study upon which it is based (*i.e.*, zebra finch) failed to reach a definitive oral LD_{50} because birds regurgitated the dose. Because this regurgitation followed a dose-dependent response (with 20%-100% of the birds regurgitating at 80 mg a.i./kg bw and higher), regurgitation was judged to be a treatment-related response. Should such repellency be demonstrated in the wild with contaminated diet, ecologically relevant adverse effects could occur in absence of suitable (non-contaminated) forage items. Notably, 0% mortality occurred at doses of 132 mg a.i./kg-bw and lower, but 40% mortality occurred at 200 mg a.i./kg-bw, the highest dose tested. Since 100% of the birds regurgitated at this dose level, the actual exposure may be substantially lower and thus, the LD_{50} in absence of regurgitation may be lower than the highest dose tested. The conduct of another acute, dose-based study (or as an alternative, a dietary study) with passerines in which regurgitation was avoided would address this source of uncertainty in the avian acute risk estimation. In such a study, the acute oral LD_{50} would have to be greater than 560 mg a.i./kg bw in order for acute risks concerns to listed species not to be triggered (*i.e.*, RQ < 0.1).

For mammals, chronic risk concerns were identified based on reproductive effects identified at 24.6 mg/kg/d from a 2-generation reproductive toxicity study with the rat and modeled EECs for mammalian forage items. Based on the refined chronic dose-based RQ values presented in **Table 36,** chronic risk concerns were identified for all of the proposed sulfoxaflor uses for at

least one dietary category which comprises four separate pesticide application scenarios. Chronic risk concerns were also identified for at least one dietary item with all size classes modeled (15, 35 and 1000g). However, it should be noted that a significant uncertainty associated with these chronic, dose-based RQ values pertains to the duration over which chronic effects to mammals are likely to be manifest. Specifically, these RQ values are derived using the maximum peak concentration of sulfoxaflor that is predicted to occur on dietary items. With a foliar half life of 12.3 days, predicted residues of sulfoxaflor on short grass would decline from a peak of 53.4 ppm (associated with an RQ of 3.8 for 15g mammal) to 14 ppm (associated with an chronic dose-based RQ of 1 for 15g mammal) in about 23 days. Over the 365 days in the T-REX simulation, predicted residues of sulfoxaflor remain above the 14 ppm level (> RQ of 1) for 30 days.

5.2.3.2. Risks to Terrestrial Plants

Risks to terrestrial plants from the proposed uses of sulfoxaflor are not expected based on available toxicity data which indicates that at or above the maximum application rate, no deleterious effects on plants was observed. This risk conclusion is also supported by the mode of action of sulfoxaflor, which would not be expected to affect plants at levels that would affect target insects.

5.2.3.3. Risks to Bees

a) Tier 1 Risk Assessment

As indicated in **Section 5.1.3.5 (Risk Estimation for Bees)**, the Tier 1 risk estimation indicates a potential risk to bees at the individual (organism) level through the acute, oral route of exposure using the maximum residues reported from available residue studies. Specifically, risks above the proposed acute risk LOC value were identified for all castes of bees modeled with the oral route of exposure (**Table 44**). Acute oral RQ values range from 0.8 to 5.7 across all castes of adult worker and larval bees examined.

A number of uncertainties associated with the Tier 1 risk estimation for sulfoxaflor are noted and further described in this section, with attention to how they may affect the tier 1 risk conclusion. These include:

- use of maximum residue reported in pollen and nectar to represent exposure to all bee casts and all crops
- lack of chronic toxicity data for adult and larval bees (and longer-term exposure to pupae)
- selection of the toxicity endpoint from the larval toxicity test (*e.g.*, NOAEC vs. LD_{50})
- accuracy of consumption rate estimates used for various bee castes
- variation in pesticide residues in pollen and nectar
- conservation of pesticide dose from plant tissue to the hive

Use of Maximum Reported Residues. As described in **Section 5.1.3.5**, the Tier 1 risk assessment for bees is based on the maximum reported residue of sulfoxaflor in pollen and nectar (6.6 and 1.0 ppm, respectively). These values were obtained from the cotton residue study using

application rates ranging from 0.045 to 0.134 lb a.i./A. Plots of this residue data are shown in **Figure 17** for sulfoxaflor residues in plant pollen (**Panel A**), forager-collected pollen (**Panel B**), and forager-collected nectar **(Panel C)** over the 10-d residue collection period.
For plant pollen, applications were made on Day 0 (all treatments) and Day 5 (three treatments). Residue data shown in **Panel A** of **Figure 17** indicate a rapid decline in sulfoxaflor concentrations in cotton pollen immediately following pesticide applications. This steep decline may be related to cotton flowers remaining open for pollination for approximately 1 day followed by withering, closure and drying on subsequent days (Ritchie *et al*., 2004; Smith, 2012). Therefore, samples taken from flowers between application days would represent flowers that were closed prior to pesticide applications. It is also worthy to note that an expected treatment-dependent trend in residue concentrations in plant pollen was not consistently seen in this study. This suggests that these data are subject to sources of variation that mask the expected trend of higher residues in plant pollen with higher pesticide application rate. Although selection of the maximum residue in plant pollen for Tier 1 risk assessment may reflect a level of conservatism in the assessment, the high variability in residue concentrations suggest that even the maximum observed concentration in pollen may not reflect the overall maximum residue in cotton plant pollen. Furthermore, results from sulfoxaflor residues measured in forager-collected pollen (**Panel B**) demonstrate that bees were repeatedly collecting pollen with 1-2 ppm. Use of these values instead of the 6.6 ppm maximum for pollen consumption would not alter the Tier 1 risk conclusions.

Regarding the selection of the maximum residue reported in nectar (1.0 ppm from hive 1 at2 x 0.134 lb a.i./A; **Appendix D**), results from **Figure 17 (Panel C)** indicate that this value is about an order of magnitude greater than the next highest concentration measured in nectar. Results shown in **Panel C** of **Figure 17** reflect mean values across two hives. Unexpectedly, this maximum concentration in nectar occurred in between application days (day 8), which likely reflects systemic translocation of sulfoxaflor from the prior applications on days 0 and 5. If the next greatest concentration of sulfoxaflor in nectar were used instead of the overall maximum (e.g., 0.1 vs. 1.0 ppm), risks to larvae would be below LOCs but those for adult foragers would still exceed the LOC of 0.4.

Lack of Chronic Toxicity Data. Another uncertainty in the Tier 1 risk assessment is lack of chronic toxicity endpoints for adult and larval bees. Although the submitted toxicity tests for honey bee larvae were intended to provide such information, limitations in the study design precluded use of results from beyond day 7 of these studies. Therefore, to the extent that adults and larvae are more sensitive to sulfoxaflor over greater exposure durations, results from this Tier 1 risk assessment will underestimate chronic risk to bees.

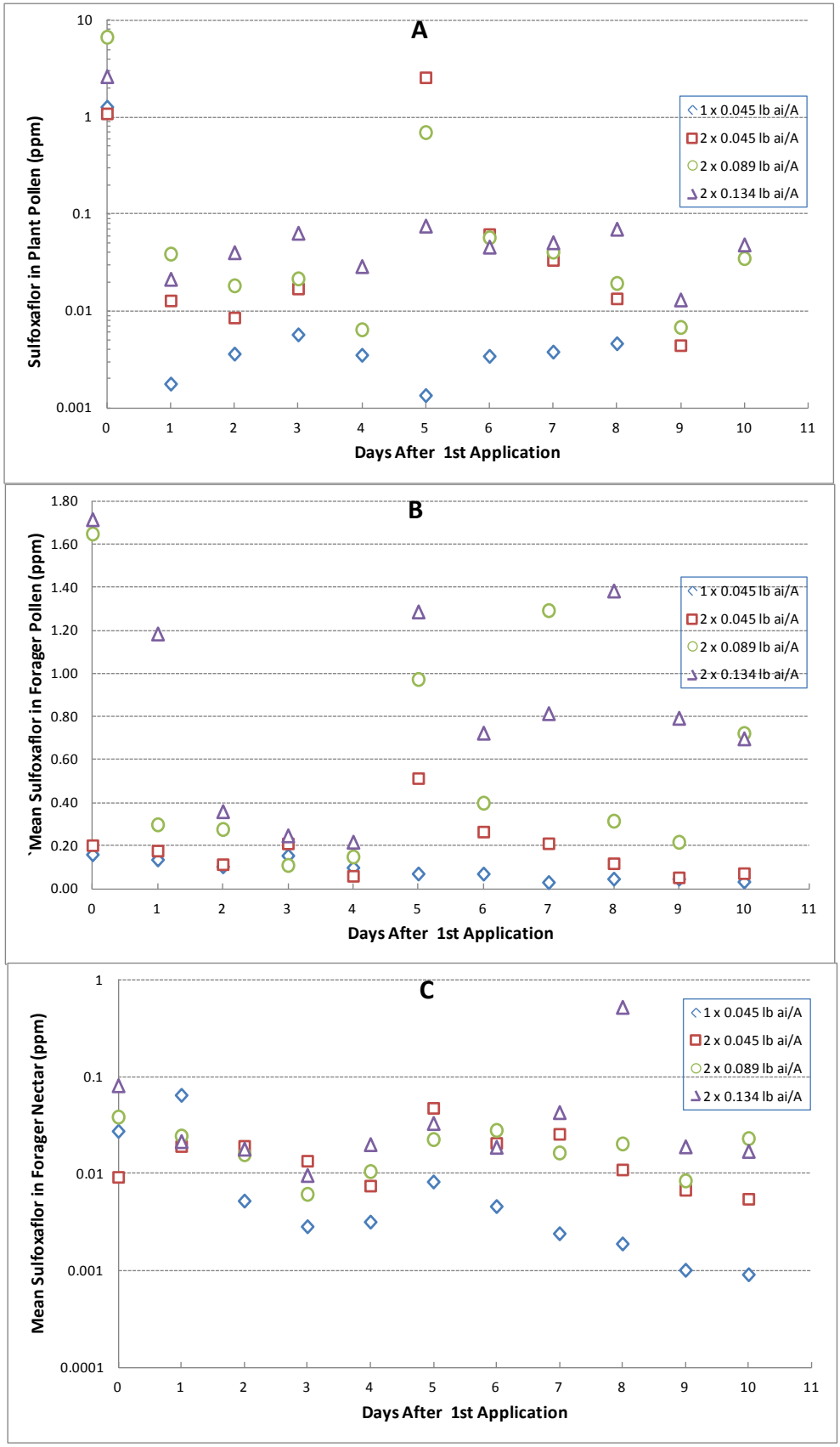


Figure 17. Sulfoxaflor residues in cotton plant pollen (A), forager-collected pollen (B) and forager collected nectar (C). Forager-collected pollen and nectar residues are a mean from bees at two hives in each tunnel (MRID 48755606).

Selection of Larval Toxicity Endpoint. As noted in Section 4, the larval toxicity endpoint selected for this analysis is >0.2 ug ai/bee. This value is a "non-definitive" LD_{50} because mortality at the highest test concentration (45%) did not exceed 50%. Although use of this non-definitive LD_{50} value introduces some uncertainty in the Tier 1 risk assessment, the close proximity of the mortality response (45%) to 50% suggests that the actual LD_{50} value would likely be relatively close to the 0.2 ug ai/bee value used in the assessment. The 7-d LD_{50} value would have to be more than a factor of 2 lower than 0.2 in order to change the risk conclusions for larval bees.

Consumption Rates of Pollen and Nectar. The consumption rate estimates of pollen and nectar used for Tier 1 risk assessment are subject to considerable variability and uncertainty, as described in USEPA (2012). However, values represent median estimates (rather than high-end) in order to avoid compounding multiple conservative assumptions on the risk assessment results. Since nectar consumption rates drive the Tier 1 risk estimates for adult nectar foragers, the consumption rate would have to be more than 14 times lower than the 292 mg/day used in this risk assessment (less than 20 mg/day) in order for RQ values to be below the proposed LOC of 0.4.

Variability in Residue Concentrations. One source of uncertainty in the Tier 1 risk assessment for honey bees relates to the variability in reported sulfoxaflor concentrations in pollen and nectar following foliar applications. Besides the overall high variability is observed in residue concentrations over time, reported concentrations in pollen and nectar do not consistently exhibit an expected proportional increase with pesticide application rate **(Figure 17).** With plant collected pollen, the maximum concentration on Day 0 occurred in the second highest treatment (2 x 0.089 lb a.i./A) while that for Day 5 occurred for the third highest treatment (2 x 0.045 lb a.i./A). In terms of average concentrations of pesticide, similar inconsistencies in proportionally of residues with pesticide application rate are apparent (**Figure 18**). For example, mean residues in plant pollen associated with the highest application rate (2 x 0.134 lb a.i./A) are about one third of corresponding mean residues from the next lower application rate (2 x 0.089 lb a.i./A). The reason for this lack of expected proportionality of pesticide concentrations in pollen is not understood and introduces uncertainty in that reliability of scaling pesticide residues according to application rate.

Conservation of Pesticide Dose. Another uncertainty associated with the Tier 1 risk assessment (particularly for larval bees) is the assumption that storage and processing of pollen and nectar by bees does not reduce pesticide exposure to brood. In the cotton study, residues in pollen collected from the comb were generally lower than that from plants or foragers. However, the maximum overall residue reported was 1.2 ppm from day 5 of the second highest treatment (2 x 0.089 lb ai//A) which is similar to the overall maximum reported in plant pollen (6.6 ppm). This suggests that at least in terms of overall maximum concentrations, the assumption that residues in pollen collected outside the comb are similar to pollen stored inside the comb does not appear to be unreasonably conservative.

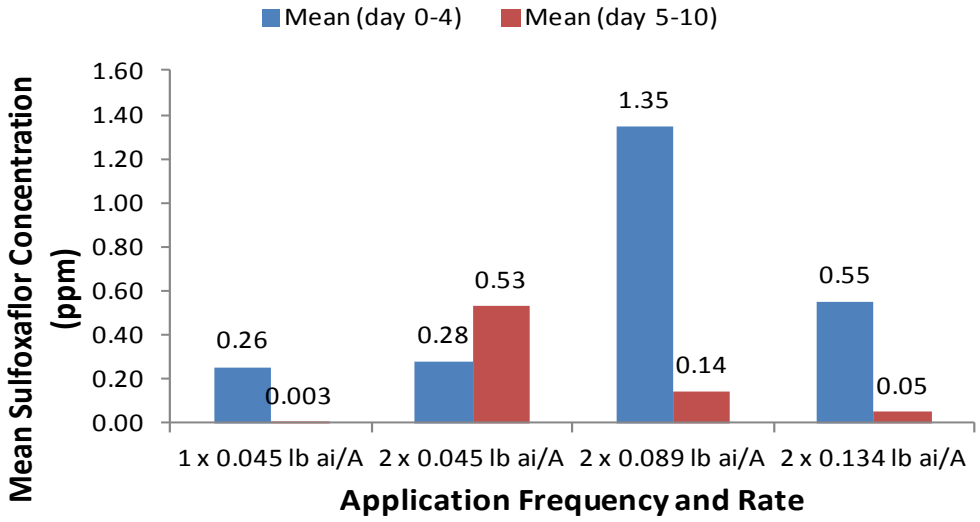


Figure 18. Mean sulfoxaflor residues in plant-collected cotton pollen over different application intervals (MRID 48755606)

b) Tier 2 Risk Assessment

A total of six Tier 2 semi-field (tunnel) studies were submitted by the registrant examining the effects of sulfoxaflor on the honey bee at the colony-level. These studies are relevant to this assessment because results of the Tier 1 risk assessment indicate a potential risk to individual adult and larval honey bees (**Section 5.1.3.5**). As noted previously, there are uncertainties associated with the results of Tier 1 assessment because effects are assessed at the level of the individual bee under controlled laboratory conditions. By quantifying effects at the whole colony level, Tier 2 studies incorporate the combined impact of a chemical stressor (*e.g.*, sulfoxaflor) on honey bee castes and their numerous inter-dependent and potentially compensatory functions within the hive. Furthermore, semi-field exposure of bees to the pesticide is controlled to a significant extent in that bees are forced to forage on treated crop due to confinement in the mesh tunnel. Although semi-field tunnel studies are advantageous in these and other aspects relative to laboratory toxicity studies on individual bees, they also have significant limitations. One limitation includes the relatively short time span that bees can be exposed within the tunnels due to stress associated with confinement (generally no more than 7-14 days). The adequacy of the forage base (nectar, pollen) is considered suboptimal compared to the diverse array of pollen and nectar sources available in natural settings where bees can forage freely. Despite these limitations, semi-field tunnel studies are considered an important line of evidence for evaluating the effects of pesticides on bees at the whole colony level.

The salient features and primary risk conclusions associated with each of the six semi-field studies are summarized in **(Table 47).** A discussion of measured effects of sulfoxaflor on various individual and colony-level endpoints is provided below. Additional details of each study are provided in **Appendix D**.

Study Design Summary. All six tunnel studies differed substantially in their overall design. For example, Hecht-Rost (2009) used a regression-type design which included five different application rates ranging from 0.006 to 0.088 lb ai/A with one replicate (tunnel) per treatment. Similarly, Ythier (2012) evaluated four different application rates ranging from 0.045 to 0.134 lb ai/A) with one replicate tunnel per treatment. The studies by Schmitzer (2010; 2011a,b,c) used a hypothesis-based test design with fewer treatments but three replicate tunnels per treatment with application rates ranging from 0.004 to 0.043 lb a.i./A. Although this design permitted statistical analysis via hypothesis testing, the high variability in response endpoints combined with the small number of replicates (3) resulted in low statistical power for detecting potential treatment-related effects in the vast majority of comparisons. Therefore, observed differences in mean responses across treatments are also emphasized in addition to statistical differences to determine whether any trends were apparent across treatments/controls.

Regarding the timing of pesticide applications, Schmitzer (2010) evaluated sulfoxaflor applications during and after bee flight, while Schmitzer (2011a,b) evaluated applications prior to bloom in addition to during and after bee flight. Schmitzer (2011c), Ythier (2012), and Hecht-Rost (2009) evaluated applications only during bee flight.

The duration of the observation period post-application also differed widely across studies. Hecht-Rost (2009) and Schmitzer (2010) included no observations after hives were removed from the exposure tunnels. Schmitzer (2011a,b,c) included a 10-d, 17-d and 90-d post tunnel (post-exposure) observation period, respectively. Ythier (2012) evaluated effects after 7 days post exposure.

It is also important to note that the time of year when each study was initiated also differed among the studies. Tests were started in June (for Schmitzer 2011a), July (for Schmitzer 2011b), August (for Hecht-Rost 2009, Schmitzer 2010, and Ythier 2012) and October (for Schmitzer 2011c). Since honey bee colonies typically show strong seasonal increases and declines over the course of spring, summer and fall, the timing of the study can be an important factor to consider when interpreting the results.

Lastly, in terms of the relevance of the foliar applications to the proposed registration of sulfoxaflor in the US, it is noted that all but the Ythier (2012) study used application rates that were substantially below the maximum proposed application rate in the US (*i.e.,* below single rate of 0.133 lb ai/A and the yearly maximum rate of 0.266 lb ai/A).

Forager Mortality. Five of the semi-field studies summarized in **Table 47** and **Appendix D** included measures of forager bee mortality determined from observations of dead bees collected away the hive and from dead bee traps at the hive entrances during the period of confinement in the tunnels. In general, the mortality pattern of adult forager bees was similar across the five tunnel studies. A spike in mortality up to 20 times that of control hives was observed on the day of pesticide application (0 day after application; 0DAA). Subsequent to 0DAA, forager bee mortality declined sharply and recovered to levels similar to control hives within 3 days, sometimes less. For studies that included identical application rates during and after bee flight (Schmitzer 2010; 2011a,b), the magnitude of forager bee mortality was generally greater when

pesticide was applied during bee flight compared to after bee flight, likely reflecting the combined effect of exposure via direct contact and via contact and/or ingestion residues on plants. The lack of sustained mortality of adult foragers following pesticide applications at rates from 3-67% of the maximum single rate proposed in the US suggests that the direct effects of sulfoxaflor on foraging bees (*i.e.*, those effects resulting from exposure from direct contact with spray droplets and residues on plants) are relatively short-lived. However, the potential for indirect effects of short-term loss of foragers on brood development and colony strength over the longer-term (e.g., through pre-mature recruitment of hive bees into the forager work force) at maximum US application rates has not been quantified. Although Ythier (2012) used the maximum single and seasonal application rates, they did not quantify the effects of sulfoxaflor on forager bee mortality since this study was intended to measure sulfoxaflor residues in plant tissues, not biological effects.

In the context of toxicity from dried residues on plants, the lack of sustained mortality to forager bees from residues applied after bee flight is consistent with the results from the foliar residue toxicity study (MRID-47832512) which showed ≤15% mortality after exposure to aged foliar residues from 4 hr to 24 hours.

Forager Flight Activity. The effect of sulfoxaflor on forager bee flight activity generally reduced the activity immediately following pesticide application. Hecht-Rost (2009), Schmitzer (2010) and Schmitzer (2011a, b) all reported reductions in flight activity up to 5 times lower than controls on 0DAA. By 3DAA, however, flight activity was similar to control levels in these studies. No obvious treatment-related effects on flight activity were reported by Schmitzer (2011c); however, the application rates used were very low relative to the proposed maximum US rate (3-16% of the maximum proposed rate). Overall, these results suggest that at rates from 3-67% of the maximum single rate proposed in the US, the direct effects of sulfoxaflor on flight activity of foraging bees (*i.e.*, those effects resulting from exposure from direct contact with spray droplets and residues on plants) are relatively short-lived. The effects of sulfoxaflor on the flight activity of foraging bees at maximum application rates proposed in the US have not been quantified.

Behavior Abnormalities. Similar to adult forager mortality and flight activity, the occurrence of behavior abnormalities (*e.g.* uncoordinated movement, spasms or an intensive cleaning behavior) was short-lived at the studied application rates (3-67% of US maximum). The frequency of these behavioral abnormalities was relatively low and they were not sustained beyond 2 days after pesticide application.

Brood Development. The suitability of the submitted semi-field studies for quantifying the effects of sulfoxaflor on developing honey bee brood is very limited, even when they are considered apart from limitations associated with the use of low application rates. Hecht-Rost (2009) and Schmitzer (2010) evaluated brood after only 7 and 9 days exposure, which is far short of the recommended duration of semi-field studies by OECD Guideline 75. A longer post-exposure evaluation time is necessary in order to evaluate the effects over an entire honey bee brood cycle (21 days for workers). Furthermore, these two studies also held bees in tunnels for much longer than recommended prior to exposure (8-11 days vs. 2-3 days recommended by

OECD Guideline 75), which may have confounded interpretation of brood development results as colony bees may have experienced undue stress from prolonged confinement of hives in the tunnel. Schmitzer (2011c) included a long post-exposure observation period (3 months); however, the study was initiated in late October and brood development and colony-strength were already in a state of significant decline due to the late season in which the study was conducted. This uncertainty is supported by the lack of discernible effects on brood at 14DAA by either reference toxicant (dimethoate or fenoxycarb) used in the study. Ythier (2012) evaluated brood pattern at 10DAA and 17DAA (close to an entire brood cycle), but did not include a control treatment in order to make appropriate comparisons. It is noted, however, that this study was not designed to provide a comprehensive evaluation of biological effects; rather it was designed to quantify sulfoxaflor residues in various plant matrices. Although pre- and post-application assessments of brood can be compared (**Table 47**), it is not possible to distinguish the effects of tunnel confinement from those of sulfoxaflor on brood development based on pre- and post-exposure comparisons alone. Adverse effects resulting from tunnel confinement in the cotton study by Ythier (2012) is considered possible (if not likely) because cotton pollen is known to be a sub-optimal source of pollen to honey bees (Vaissiere *et al.*, 1994) and bees were not able to maintain sufficient pollen stores over the course of the tunnel exposure.

Apart from their low applications rates (16-32% of the proposed US maximum), the two studies with the most suitable design for evaluating the effects of sulfoxaflor on honey bee brood are Schmitzer (2011a,b). Both studies included adequate post-application observation periods (20-53 days), used three replicates/treatment, and tracked the development of a defined cohort of marked brood over time (rather than overall brood pattern on the comb). By following the development of individual brood, two indices of brood development were derived (*i.e.*, brood termination index and brood compensation index) according to OECD Guideline 75. The brood termination index is simply the proportion of brood that fails to develop fully through emergence. The brood compensation index is a reflection of the average of the five development stages achieved by the brood cohort (with 1 = egg, 2 = young larvae, 3 = old larvae, 4 = pupae, 5= empty cell [emerged] or cell re-filled with egg/larva).

In both studies, Schmitzer (2011a,b) reported a high average brood termination rate in control hives of 56% and 65%, respectively. This means that over half the brood in control hives failed to emerge and transition to adult bees. Although no specific acceptability criteria have been defined by OECD for this index in controls, these values exceed brood termination rates of controls reported by an inter-laboratory study supporting the development of OECD Guideline 75 (Schur *et al*., 2003). Notably, Schur *et al.* reported that brood termination rate in control hives varied from 8% to 43% in a ring-test of five trials of the OECD 75 tunnel study design. The authors attributed the high brood termination rates (32-43%) in three trials to poor weather conditions that occurred during the studies. In a recent review of historical control data for brood termination rate, Pistorius *et al*., (2011) correlated increases in control brood termination rate with lateness in the season of test initiation and smaller available forage area in the tunnels. Regardless of the source of the high brood termination rate in the control treatments from Schmitzer (2011a,b), it likely reflects stress on the bees caused by the study design and creates substantial uncertainty as to the ability to detect the potential effects of sulfoxaflor on developing brood. A large increase in brood termination rate (98-100%) was observed for the reference

toxicant (fenoxycarb) for these two studies, which indicates that despite the high larval mortality in control hives, a major catastrophic impact on brood could be detected. Importantly, the application rates of fenoxycarb (300 g ai/ha or about 2X the maximum single application rate identified in the US) are specifically intended to cause catastrophic impacts on developing brood in order to demonstrate that the study design was sufficient to detect effects on brood. Although the effects of sulfoxaflor applications on brood development are uncertain due to high mortality of larvae in controls, these results suggest that the overall effects were less than the catastrophic losses experienced by the colonies exposed to the reference toxicant.

The results from the brood compensation index indicated no obvious or statistical differences in treatments compared to controls by 22DAA and 21DAA for Schmitzer (2011a,b), respectively. The average brood compensation rate in control and sulfoxaflor-treated hives ranged from 3.0 to 4.2. This indicates that on average, honey bee broods were able to reach an older larval or pupal stage. Therefore, these results suggest that the high brood termination rate discussed previously occurred principally at the latter stages of brood development. Since the brood compensation and termination indices are related, the uncertainty associated with high brood termination rate in controls also impacts the interpretation of the brood compensation index responses. In both studies, a large reduction in brood compensation index (1.7-1.9) indicates the effects of the reference toxicant (fenoxycarb) were discernible in this study.

Taken as a whole and in consideration of their respective limitations, the results from the six tunnel studies are unable to conclusively demonstrate whether sulfoxaflor applications adversely impact brood development, even at the lower application rates used.

Colony Strength. Measures of colony strength (number of bees occupying the combs) were available from 5 of the 6 tunnel studies submitted (**Table 47**). Assessment relative to concurrent control hives was possible in 3 studies (one study had no concurrent control and the other had compromised controls). In general, effects of sulfoxaflor on colony strength were slight or not apparent with the three studies with controls (Schmitzer 2011a,b,c). A 15-28% reduction in mean colony strength was apparent through most of the exposure period for the treatment with the two highest application rates (0.043 lb ai/A pre-bloom and after flight). However, a similar study conducted by the same authors (Schmitzer 2011b) found no obvious difference in colony strength with 0.043 lb ai/A applied pre-bloom. Similarly, Schmitzer (2011c) found no obvious difference in colony strength of treatments compared to controls by 14DAA. However, it should be noted that application rates used in this study were very low (3-16% of US maximum) and it was conducted late in the season as colonies were in a natural state of decline in terms of brood production.

When colony strength is evaluated by comparing pre- and post-application measurements within a sulfoxaflor treatment, no treatment-related difference is apparent in the study by Hecht-Rost (2009) measured at 7DAA or Ythier (2012) measured at 10 days after first application (10DAFA and 17DAFA. The similarity in colony strength measurements taken pre- and post application within and among all treatments reported for the cotton study (Ythier 2012) implies that conditions of the sulfoxaflor treatments did not result in an obvious decline in mean colony strength by 17DAFA, even at the maximum US application rate of 2 x 0.134 lb ai/A. Although

lack of a current control and limited observation period precludes definitive conclusions regarding the effect of sulfoxaflor on colony strength in this study, these results suggest that major impacts on honey bee colony strength are not apparent with sulfoxaflor applications at the maximum US application rate, at least over the short term (*e.g.,* 17DAFA).

Overall Conclusions from Tier 2 Assessment. Results from the Tier 2 semi-field studies suggest that at the application rates used (3-67% of US maximum), the direct effects of sulfoxaflor on adult forager bee mortality, flight activity and the occurrence of behavioral abnormalities is relatively short-lived, lasting 3 days or less. Direct effects are considered those that result directly from interception of spray droplets or dermal contact with and ingestion of foliar residues. The direct effect of sulfoxaflor on these measures at the maximum application rate in the US is presently not known. The effect of sulfoxaflor on brood development is considered inconclusive due to the aforementioned limitations associated with these studies. When compared to controls, the effect of sulfoxaflor on colony strength applied at 3-32% of the US maximum proposed rate was either not apparent or modest at most (based on one study). Sulfoxaflor applied to cotton foliage up to the maximum rate proposed in the US did not result in an observable decline in mean colony strength by 17DAFA when compared to colonies assessed 3 days prior to application. Additional data would be needed to determine the potential effects of sulfoxaflor applications on brood development and long-term colony health at the maximum application rates proposed in the US. Such data would include one or more Tier 2 semi-field tunnel studies conducted according to OECD 75 guidance. It is further noted that the high variability in sulfoxaflor residues from the cotton residue study and the nature of the cotton flowering introduces uncertainty in the extrapolation of these residue results to other crops. Therefore, additional data on the nature and magnitude of sulfoxaflor residues in one or more pollinator-attractive crops would be needed to address this source of uncertainty.

Table 47. Summary of Tier 2 colony-level studies conducted with sulfoxaflor

Study Attribute	Results Summary					
	1. Hecht-Rost (2009) MRID-48445806	**2. Schmitzer (2010)** MRID 48445807	**3. Schmitzer (2011a)** MRID 48755604	**4. Schmitzer (2011b)** MRID 48755605	**5. Schmitzer (2011c) (no MRID)**	**6. Ythier 2012** MRID 48755606
Application Timing & Rate	**During flight: 0.006-0.088 lb ai/A** (6-99 g ai/ha)	**During flight: 0.021-0.043 lb ai/A** (24 & 48 g ai/ha) **After flight:** 0.043 lb ai/A (48 g ai/ha)	**Pre bloom: 0.043 lb ai/A** (48 g ai/ha) **After flight: 0.021-0.043 lb ai/A** (24 & 48 g ai/ha) **During flight: 0.021 lb ai/A** (24 g ai/ha)	**Pre bloom: 0.043 lb ai/A** (48 g ai/ha) **After flight: 0.021 lb ai/A** (24 g ai/ha) **During flight: 0.021 lb ai/A** (24 g ai/ha)	**During flight: 0.004, 0.007, 0.021 lb ai/A** (4, 8, 24 g ai/ha)	**During flight**: **0.045 lb ai/A x 1** (50 g ai/ha x 1) **0.045 lb ai/A x 2** (50 g ai/ha x 2) **0.089 lb ai/A x 2** (100 g ai/ha x 2) **0.134 lb ai/A x 2** (150 g ai/ha x 2)
No. Reps. / Treatment	1	3	3	3	3	1
% of US Max. Single Appl. Rate	4-67%	16-32%	16-32%	16-32%	3-16%	34-100%
Crop	*Phacelia*	*Phacelia*	*Phacelia*	*Phacelia*	*Phacelia*	Cotton
Exposure Pathways Assessed	Direct contact, dermal, oral	Direct contact, dermal, oral	**During flight:** Direct contact, dermal, oral **Pre-bloom, after flight:** dermal, oral	**During flight:** Direct contact, dermal, oral **Pre-bloom, after flight:** dermal, oral	Direct contact, dermal, oral	Direct contact, dermal, oral

Study Attribute	Results Summary					
	1. Hecht-Rost (2009) MRID-48445806	**2. Schmitzer (2010)** MRID 48445807	**3. Schmitzer (2011a)** MRID 48755604	**4. Schmitzer (2011b)** MRID 48755605	**5. Schmitzer (2011c) (no MRID)**	**6. Ythier 2012** MRID 48755606
Exposure Duration, Month of Study Initiation	**In-Tunnel Exposure:** (pre-application) **11d** (post-application) **7d** **Post Tunnel Obs.:** **0d** August	**In-Tunnel Exposure:** (pre-application) **8d** (post-application) **9d** **Post Tunnel Obs.:** **0d** August	**In-Tunnel Exposure:** (pre-application, after & during flight) **3d** (pre-application, pre-bloom) **0d** (post-application, after & during flight) **7d** (post-application, pre-bloom) **10d** **Post Tunnel Obs.:** **20d** June	**In-Tunnel Exposure:** (pre-application, after & during flight) **10d** (pre-application, pre-bloom) **0d** (post-application, after & during flight) **7d** (post-application, pre-bloom) **17d** **Post Tunnel Obs.:** **53d** July	**In-Tunnel Exposure:** (pre-application) **8d** (post-application) **7d** **Post Tunnel Obs.:** **90d (colony survival)** October	**In-Tunnel Exposure:** (pre-application) 3**d** (post-application) **10d** **Post Tunnel Obs.:** **7d** August-September
Forager Mortality	**Day 0**: up to 7X increase (treatment dependent) **Day 3-7**: ≈ control levels;	**Day 0**: Up to 20X increase **Day 3-7**: ≈ control levels	**Day 0-1**: up to 8X increase in mortality **Days 2-7**: treat ≈ controls **Days 8-27 (post tunnel):** treat ≈ controls	**Day 0**: up to 3X ↑ **Days1-7:** no consistent difference vs. controls**	**Day 0:** up to 4X ↑; **Day 1-7:** treatments ≈ controls	Not assessed
Flight Intensity	**Day 0**: up to 5X decrease (dose-dependent) **Day 3-7**: Dose-independent decrease	**Day 0**: up to 2X decrease **Days 1-7**: treatment ≈ controls	Some reduction seen (during and after bee flight), but recovery to control levels by D2-4	**Day 0:** some (<50%) reduction vs. controls **Day 1-7:** treatment ≈ controls	No obvious treatment related effects on foraging activity, but late season may have confounded results	Not assessed
Forager Behavior	Light intoxication symptoms (D0AA only**)**	Some behavioral abnormalities ≤ 2DAA	Some behavior abnormalities observed on 0DAA in 1 treatment, none thereafter	No behavioral abnormalities observed at any treatment	Some behavior abnormalities observed on 0DAA in 24 g ai/ha, none thereafter	Not assessed

Study Attribute	Results Summary					
	1. Hecht-Rost (2009) MRID-48445806	**2. Schmitzer (2010)** MRID 48445807	**3. Schmitzer (2011a)** MRID 48755604	**4. Schmitzer (2011b)** MRID 48755605	**5. Schmitzer (2011c) (no MRID)**	**6. Ythier 2012** MRID 48755606
Brood Development	**Treat vs. Control:** Inconclusive **Pre vs. Post Appl.:** - Dose-dependent ↓in % Larvae - Dose-independ. ↓ in % capped brood	**Treat vs. Control:** - no statistical or obvious difference @ 9DAA; **Pre vs. Post:** - no statistical or obvious differences; - modest ↓% capped and ↑ % empty cells may reflect emergence	**Treat vs. Control:** **Brood compensation index:** - no statistical or obvious treatment related effects @ 22DAA - **Brood termination rate:** - inconclusive	**Treat vs. Control:** **Brood compensation index:** - no statistical or obvious treatment related effects @ 21DAA - **Brood termination rate:** - inconclusive	**Treat vs. Control:** **Brood pattern:** treat ≈ controls through 14DAA, but late season may have confounded results	No control was included **Pre vs. Post Appl.** **Brood pattern:** - %larvae, %pupae, reduced ~ 2X @ 10DAA; - % pollen ~ 0% @ 10DAA - %nectar ≥ pre-appl. levels - % adult bees within 20% of pre-appl levels
Colony Strength	**Treat vs. Control:** Inconclusive **Pre vs. Post Appl.:** 10-25% dose-independent ↓	Not assessed	**Treat vs. Control:** Up to 15-28% reduction in 48g ai/ha through 27DAA (pre bloom) and 15DAA (after flight)	**Treat vs. Control:** - treatments ≈ controls up through 60DAA	**Treat vs. Control:** - treatments ≥ controls, but late season may have confounded results - By D90AA, only 1/18 colonies failed (8 g/ha)	**Pre vs. Post Appl.** Hive strength similar across treatments before and after application
Study Limitations*	1. *Varroa* infestation in controls 2. Long pre-exposure period in tunnels (11d) 3. High variability among colonies prior to exposure 4. Short observation period (7d) 5. 1 rep/treatment 6. Low % larvae in controls (7DAA)	1. Long pre-exposure period in tunnels (8d) 2. Short observation period (9d) 3. High overall variability within treatments (n=3) 4. No colony strength measurements	1. Poor control performance re: brood termination rate (56%) 2. High overall variability within treatments (n=3)	1. Poor control performance re: brood termination rate (65%) 2. Long pre-exposure period in tunnels (10d) 3. high overall variability within treatments (n=3)	1. All colonies in steep decline in brood condition due to late season (Oct). rendering the ability to detect treatment effects uncertain	1. No concurrent control was included for interpreting biological effects*** 2. one replicate / treatment 3. short observation period (17d)

Study Attribute	Results Summary					
	1. Hecht-Rost (2009) MRID-48445806	**2. Schmitzer (2010)** MRID 48445807	**3. Schmitzer (2011a)** MRID 48755604	**4. Schmitzer (2011b)** MRID 48755605	**5. Schmitzer (2011c) (no MRID)**	**6. Ythier 2012** MRID 48755606
Reference Toxicant Effects	**Dimethoate (400g/ha);** - similar brood pattern as controls (except % larvae) - colony strength similar to treatments; - sustained ↑in # dead bees; -sustained ↓flight intensity	**Dimethoate (600g/ha);** - similar brood pattern as controls - sustained ↑in # dead bees; -sustained ↓flight intensity	**Fenoxycarb (300g /ha)** - **Brood compensation:** sustained ↓ vs. controls over 22DAA - **Brood termination:** major impact (98%) - c**olony strength:** generally sustained reduction vs. controls	**Fenoxycarb (300g /ha & Dimethoate 600g/ha:** - c**olony strength:** generally sustained ↓ - **brood compensation:** sustained ↓ - **Brood termination:** major impact (98-100%)	**Dimethoate (600g/ha), Thiamethoxam (50g /ha)**: - Brood pattern: similar to controls through 14DAA	Not assessed

***** Except for Ythier (2012), these limitations are in addition to the use of application rates below the proposed U.S. maximum single rate of 0.133 lb ai/A

** 1 of 3 tunnel replicates at 48 g ai/ha showed increased mortality over days 1-7AA, but it is uncertain if this is treatment related.

*** this study was designed to assess residues of sulfoxaflor in plant and hive matrices, not biological effects.

Overall Bee Risk Assessment Conclusions:

In considering multiple lines of evidence, including results of Tier 1 risk assessment, the mode of action of sulfoxaflor, the nature of its uptake and persistence in plant tissues, and results (and limitations) of the Tier 2 studies, the potential impact of the proposed uses of sulfoxaflor at maximum application rates on developing bee brood and colony strength cannot be precluded.

5.2.4 Review of Incident Data

Incident reports submitted to EPA since approximately 1994 have been tracked by assignment of EIIS (Environmental Incident Information System) in an Incident Data System (IDS). Over the 2012 growing season, a Section 18 emergency use was granted for application of sulfoxaflor to cotton in four states (MS, LA, AR, TN). To date, no incident reports have been received in association with the use of sulfoxaflor. However, due to the nature of ecological incident reporting, absence of incidents cannot be construed with absence of incidents.

5.2.5 Endocrine Effects

Under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA), EPA is required to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen- and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, and the FFDCA authority to require the wildlife evaluations. As the science develops and the resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). When the appropriate screening and or testing protocols being considered under the Agency's Endocrine Disruptor Screening Program have been developed, sulfoxaflor may be subjected to additional screening and or testing to better characterize effects related to endocrine disruption.

5.2.6 Threatened and Endangered Species Concerns

For listed species assessment purposes, the action area is considered to be the area affected directly or indirectly by the Federal action and not merely the immediate area involved in the action. At the initial screening-level, the risk assessment considers broadly described taxonomic groups and so conservatively assumes that list species within those broad groups are collocated

within the pesticide treatment area. This means that terrestrial plants and wildlife are assumed to be located on or adjacent to the treated site and aquatic organisms are assumed to be located in a surface water body adjacent to the treated site. The assessment also assumes that the listed species are located within an assumed area which has the relatively highest potential exposure to the pesticide, and that exposures are likely to decrease with distance from the treated area.

If the assumptions associated with the screening-level action area result in RQs that are below the listed species LOCs, "no effect," determination conclusion may be made with respect to listed species in that taxa (for direct effects), and no further refinement of the action is necessary. Furthermore, RQs below the listed species LOCs for a given taxonomic group indicate no concern for indirect effects upon listed species that depend upon the taxonomic group as a resource. However, in situations where the screening assumptions lead to RQs in excess of the risk to listed species LOCs for a given taxonomic group, a potential "may affect," conclusion exists and may be associated with direct effects on listed species belonging to that taxonomic group or may extend to indirect effects upon listed species that depend on that taxonomic group as a resource. In such cases, additional information on the biology of the listed species, the locations of these species, and the locations of use sites could be considered along with available information on the fate and transport properties of the pesticide to determine the extent to which screening assumptions regarding an action area apply to a particular listed organism. These subsequent refinement steps could consider how this information would impact the action area for a particular listed organism and may potentially include areas of exposure that are downwind and downstream of the pesticide use site.

In conducting a screen for indirect effects, direct effects LOCs for each taxonomic group are used to make inferences concerning the potential for indirect effects upon listed species that rely upon non-listed organisms in these taxonomic groups as resources critical to their cycle. Pesticide use scenarios resulting in RQs that are below all direct effect listed species LOCs for all taxonomic groups assessed are considered of no concern for risks to listed species either by direct or indirect effects.

For sulfoxaflor, the potential direct effects to listed species should they co-occur with application sites are indicated for mammals (chronic toxicity) and birds (including terrestrial-phased amphibians and reptiles; acute toxicity), non-target terrestrial insects (using honey bee as a surrogate); freshwater benthic insects (chronic toxicity) and saltwater invertebrates (acute toxicity. Risk to listed species LOCs are not exceeded for plants. For the maximum proposed sulfoxaflor application rates, there may be a potential concern for direct effects to the following groups of organisms:

- Birds
- Mammals
- Terrestrial-phase reptiles
- Terrestrial-phase amphibians
- Terrestrial insects
- Aquatic invertebrates

A spatial co-occurrence analysis would be necessary to delineate the action area. However, given the potential widespread use of sulfoxaflor based on the proposed labels, the action area would likely encompass wide portions of the United States.

5.2.7 Description of Assumptions, Limitations, Uncertainties and Data Gaps

5.2.7.1 Exposure for All Taxa

There are a number of areas of uncertainty in the aquatic and terrestrial risk assessments. The toxicity assessment for terrestrial and aquatic plants and animals is limited by the number of species tested in the available toxicity studies. Use of toxicity data on representative species does not provide information on the potential variability in susceptibility among species to acute and chronic exposures.

For each proposed use, the risk assessment is based on the maximum application rate on the proposed label. The frequency at which actual uses approach these maximum scenarios is dependent on the resistance to the pesticide, the timing of applications, and market forces. Exposure and risks could be overestimated if the actual application rates, frequency of application, or number of applications are lower than the input parameters used for the conservative exposure scenario that was modeled

5.2.7.2 Exposure for Aquatic Species

This Tier II risk assessment relies on best available estimates of environmental fate and physicochemical properties, maximum application rate of sulfoxaflor, application frequency and interval. However, several uncertainties and model limitations are noted and should be considered in interpreting the results of this aquatic risk assessment.

- The frequency at which actual sulfoxaflor uses approach the use estimates modeled is dependent on resistance to the insecticide, timing of applications, and market forces. In general, model output values represent the upper-bound estimates of concentrations that might be observed in surface water due to the application of sulfoxaflor, given available data and model limitations.

- Major uncertainties associated with the standard runoff scenario include the physical construct of the watershed and representation of vulnerable aquatic environments for different geographic regions. The physicochemical properties (pH, redox conditions, *etc*.) of the standard farm pond are based on a Georgia farm pond. These properties are likely to be regionally specific because of local hydrogeological conditions. Any alteration in water quality parameters may impact the environmental behavior of a pesticide. The farm pond represents a well mixed, static water body. Because the farm pond is a static water body (no flow through), it does not account for pesticide removal through flow through or water releases. The lack of flow through the farm pond provides an environmental condition for accumulation of persistent pesticides. The assumption of

uniform mixing does not account for stratification due to thermoclines (*e.g.*, seasonal stratification in deep water bodies). Additionally, the dimensions of the standard runoff scenario assume a watershed area to water body volume ratio of 10 ha: 20,000m^3. This ratio is recommended to maintain a sustainable constructed pond in the Southeastern United States. The use of higher watershed area to water body volume ratios (as recommended for sustainable ponds in drier regions of the United States) may lead to higher pesticide concentrations when compared to the standard watershed area to water body volume ratio.

- The standard runoff scenario assumes uniform soils and agronomic management practices across the standard 10-hectare field. Soils can vary substantially across even small areas; this variation is not reflected in the model simulations. Additionally, the impact of unique soil characteristics and soil management practices (*e.g.*, tile drainage) are not considered in the standard runoff scenario. The assumption of uniform site and management conditions is not expected to represent some site-specific conditions. Extrapolating the risk conclusions from the standard pond scenario to other aquatic habitats (*e.g.*, marshes, streams, creeks, and shallow rivers, intermittent aquatic areas) may either underestimate or overestimate the potential risks in those habitats.

- For an acute risk assessment, there is only a one-day averaging time for exposure. Use of such a "peak" concentration, with a 1-in-10 year annual return frequency, implies that exposure is sufficient to elicit acute effects comparable to those observed over more protracted exposure periods tested in the laboratory, typically 48 to 96 hours. In the absence of data regarding time-to-toxic event analyses and latent responses to peak exposure, the degree to which risk is overestimated cannot be quantified.

5.2.7.3 Exposure for Terrestrial Species

This risk assessment relies on the best available estimates of environmental fate and physicochemical properties, maximum application rate of sulfoxaflor, maximum number of applications, and the shortest interval between applications. However, several uncertainties and model limitations are noted and should be considered in interpreting the results of this terrestrial risk assessment.

a) Location of Wildlife Species

For screening terrestrial risk assessments, a generic bird or mammal is assumed to consume 100% of its diet as treated seeds from the application site. This assumption may lead to an overestimation of exposure to species that do not occupy the treated field. The actual habitat requirements of any particular terrestrial species are not considered, and it is assumed that species occupy, exclusively and permanently, the treated area being modeled. This assumption leads to a maximum level of exposure in the risk assessment.

b) Routes of Exposure

Dietary Exposure

Screening-level risk assessments for spray applications of pesticides assume that 100% of the diet is relegated to single food types foraged only from treated fields. These assumptions are likely to be conservative for many species and will tend to overestimate potential risks when species are foraging on multiple sources of food (*i.e.*, not just treated seeds). Furthermore, while the assumption of 100% diet from a treated area may be reasonable worst case assumption for acute exposures, this assumption is likely much less applicable to long-term (chronic) exposures modeled as single food types composed entirely of treated seeds. Data on the amount of wildlife diet composed of seeds from treated fields would be needed to reduced this uncertainty.

Dermal Exposure

The screening assessment does not consider dermal exposure of terrestrial organisms to sulfoxaflor. The Agency is actively pursuing modeling techniques to account for dermal exposure via direct application of spray and by incidental contact with contaminated vegetation, soil and water.

Drinking Water Exposure

Drinking water exposure to a pesticide active ingredient may be the result of consumption of surface water or consumption of the pesticide in dew or other water on the surfaces of treated vegetation. For pesticide active ingredients with a potential to dissolve in runoff, puddles on the treated field may contain the chemical. The SIP tool (version 1.0) was used to assess the potential for exposure concerns to birds and mammals via drinking water alone. Sulfoxaflor's solubility in water (1,380 mg/L) and toxicity to avian and mammalian species are inputs for the potential upper-bound drinking water calculations. Because the test of most sensitive avian species (zebra finch) did not produce a definitive LD_{50} value, the lowest concentration tested that resulted in no significant effects was used as an upper-bound estimate of acute toxicity (>80 mg a.i./kg bw) was used as the toxicity endpoint for birds for SIP. For mammals, an LD_{50} of 1000 mg/kg bw was used (rat). Chronic NOAEC/NOAEL toxicity values used for birds and mammals are 200 ppm (mallard) and 6.07 mg/kg bw (rat). Based on this information, sulfoxaflor exposure through drinking water alone has the potential to be a relevant acute or chronic exposure route exposure route of concern for mammals or birds.

c) Incidental Pesticide Releases Associated with Use

This risk assessment is based on the assumption that the entire treatment area is subject to sulfoxaflor application at the rates specified on the label. This translates to an even seeding rate across an entire field. In reality, there is the potential for uneven application of sulfoxaflor through such plausible incidents as changes in calibration of application equipment, spillage, and localized releases at specific areas of the treated field that are associated with specifics of the type of application equipment

d) Residues in Pollen and Nectar

Residue information is available for three plant species: pumpkin, cotton and *Phacelia.* As noted previously, there are limitations in these data which contribute to uncertainty in the Tier 1 risk assessment for bees. Specifically, the pumpkin residue data reflect systemic transport only and were collected several days after pesticide application. The *Phacelia* residue data are from application rate lower than the proposed U.S. maximum and are very limited for pollen and nectar. The cotton study contains the most extensive residue information available, However, the high variability in sulfoxaflor residues from the cotton residue study and the nature of the cotton flowering (*i.e.,* open for only one day) introduces uncertainty in the extrapolation of these residue results to other crops. Therefore, additional data on the nature and magnitude of sulfoxaflor residues in one or more pollinator-attractive crops would be needed to address this source of uncertainty.

5.2.7.4 Effects Assessment for All Taxa

a) Age Class and Sensitivity of Effects Thresholds

It is generally recognized that test organism age may have a significant impact on the observed sensitivity to a toxicant. The screening risk assessment acute toxicity data for fish are collected on juvenile fish and aquatic invertebrate acute testing is performed on recommended immature age classes. Similarly, acute dietary testing with birds is also performed on juveniles, with mallard being 5-10 days old and quail at 10-14 days of age.

Testing of juveniles may overestimate the toxicity of direct acting pesticides in adults. As juvenile organisms do not have fully developed metabolic systems, they may not possess the ability to transform and detoxify xenobiotics equivalent to the older/adult organism. The screening risk assessment has no current provisions for a generally applied method that accounts for this uncertainty. In so far as the available toxicity data may provide ranges of sensitivity information with respect to age class, the risk assessment uses the most sensitive life-stage information as the conservative screening endpoint.

b) Lack of Effects Data for Amphibians and Reptiles

Currently, toxicity studies on amphibians and reptiles are not required for pesticide registration. Since these data are lacking, the Agency uses fish as surrogates for aquatic-phase amphibians and birds as surrogates for terrestrial-phase amphibians and reptiles. If other species are more or less sensitive to sulfoxaflor than the surrogates, risks may be under- or overestimated, respectively. The Agency is not limited to a base set of surrogate toxicity information in establishing risk assessment conclusions. The Agency also considers toxicity data on non-standard test species when available. Further research is needed to determine whether, in general, reptiles and terrestrial-phase amphibians are suitably represented by bird species in assessing risks for sulfoxaflor and fish are an appropriate surrogate for aquatic-phase amphibians.

c) Use of the Most Sensitive Species Tested

Although the screening-level risk assessment relies on a selected toxicity endpoint from the most sensitive species tested, it does not necessarily mean that the selected toxicity endpoints reflect sensitivity of the most sensitive species existing in a given environment. The relative position of the most sensitive species tested in the distribution of all possible species is a function of the overall variability among species to a particular chemical. The relationship between the sensitivity of the most sensitive tested species versus wild species (including listed species) is unknown and a source of significant uncertainty. In addition, in the case of listed species, there is uncertainty regarding the relationship of the listed species' sensitivity and the most sensitive species tested.

d) Brood Development and Colony-Level Effects

As described in **Section 5.2.3.3**, the results from the available semi-field tunnel studies are insufficient for concluding whether sulfoxaflor applications adversely impact brood development, even at the lower application rates used. Additional data would be needed to determine the potential effects of sulfoxaflor applications on brood development and long-term colony health at the maximum application rates proposed in the US. Such data would include one or more Tier 2 semi-field tunnel studies conducted according to OECD 75 guidance.

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MRID 47832109
Gerke A (2008). XDE-208: Whole sediment 10 day acute toxicity test with midge larvae (*Chironomus dilutus*). ABC Laboratories Inc. Company Report Number 080076

MRID 47832110
Gerke A (2008). XDE-208: Acute toxicity test to the sheepshead minnow, *Cyprinodon variegatus*, determined under static test conditions. ABC Laboratories Inc. Company Report Number 080067

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MRID 4783212
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MRID 47832113
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MRID 47832114
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MRID 47832121
Dengler D (2009). Testing of effects of XDE-208 on the single cell green alga, *Pseudokirchneriella subcapitata* in a static 96 h test. Eurofins GAB GmbH. Company Report Number 080439

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MRID 47832074
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Wildlife International Ltd. Company Report Number 070260

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MRID 48445807
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Schmitzer, S. (2011c). Toxicity Testing of GF-2626 on Honey Bees (*Apis mellifera* L.) under Semi-Field Conditions - Tunnel Test . Dow Study ID 101602

MRID 48445809
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MRID 47832102
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MRID 47832103
XR-208: acute oral toxicity test with the honeybee, *Apis mellifera.* ABC Laboratories Inc. Company Report Number 070172

MRID 47832107
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MRID 47832417
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MRID 47832418
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MRID 48755602
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MRID 48755603
Stempniewicz A (2012). XDE-208: Chronic toxicity effects to honeybee larvae (*Apis mellifera* L.) under laboratory conditions (*in vitro*). Dow Company Report Number 120536-B

MRID 48755604
Schmitzer, S. (2011a). Study on the Effect of GF-2626 on Honey Bees and their Brood (*Apis mellifera* L.) under Semi-Field Conditions - Tunnel Test. Dow Study ID 101599

MRID 48755605
Schmitzer, S. (2011b). Study on the Effect of GF-2626 on Honey Bees and their Brood (*Apis mellifera* L.) under Semi-Field Conditions - Tunnel Test. Dow Study ID 80755

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Appendix D.

Supporting Information for Honey Bee Risk Assessment

I. Individual Level Toxicity Studies

Acute Contact Toxicity of TGAI to Adult Bees

Bergfield A (2007; MRID 47832102). The acute toxicity of sulfoxaflor (purity 96.6 % w/w) to the honeybee (*Apis mellifera*) was determined after contact exposure. Adult worker bees were topically exposed to nominal doses of 0.025, 0.05, 0.1, 0.2, 0.4, 0.8 and 1.6 µg a.i./bee and observed for 72 hours. In addition, a dilution water control was tested. There was 7% mortality in the control group with dose-response mortality ranging 3-97% in the treatment groups. No sublethal effects were noted at the end of the test. The 72-hour LD_{50} was 0.379 µg a.i./bee. This study is classified as acceptable.

Acute Contact Toxicity of Formulated Product to Adult Bees

Vinall (2010; MRID 47832511). The acute toxicity of GF-2372 (water-dispersible granule, 50% w/w sulfoxaflor) to the honeybee (*Apis mellifera*) was determined after contact exposure. Adult worker bees were topically exposed to nominal doses of 0.013, 0.032, 0.08, 0.2 and 0.5 µg a.i./bee and observed for 48 hours. In addition, a wetting agent control and a water control were tested. There was 2% mortality in the wetting agent control, no mortality in the water only control, and dose-response mortality was observed in the treatment groups ranging 0-90% in the treatment groups. No sublethal effects were noted at the end of the test. The 48-hour LD_{50} was 0.224 µg a.i./bee. This study is classified as acceptable.

Vinall (2009; MRID 47832419). The acute toxicity of GF-2032 (suspension concentrate, 22% w/w sulfoxaflor) to the honeybee (*Apis mellifera*) was determined after contact exposure. Adult worker bees were topically exposed to nominal doses of 0.021, 0.047, 0.103, 0.227 and 0.5 µg a.i./bee and observed for 48 hours. In addition, a wetting agent control and a water control were tested. There was 6% mortality in both controls, and dose-response mortality was observed in the treatment groups ranging 8-98% in the treatment groups. No sublethal effects were noted at the end of the test. The 48-hour LD_{50} was 0.130 µg a.i./bee. This study is classified as acceptable.

Vinall (2009; MRID 47832418). The acute toxicity of GF-2032 (suspension concentrate, 22% w/w sulfoxaflor) to the bumblebee (*Bombus terrestris*) was determined after contact exposure. Adult worker bees were topically exposed to nominal doses of 0.01, 0.1, 1, 10 and 100 µg a.i./bee and observed for 72 hours. In addition, a wetting agent control and a water control were tested. There was 6.7% mortality in the water control, 3.3% mortality in the wetting agent control, and dose-response mortality was observed in the treatment groups ranging 3.3-100.0% in the treatment groups. No sublethal effects in surviving bees were noted. The 72-hour LD_{50} was 7.554 µg a.i./bee.

Acute Oral Toxicity of TGAI to Adult Bees

Bergfield A (2007; MRID 47832103). The acute toxicity of sulfoxaflor (purity 96.6 % w/w) to the honeybee (*Apis mellifera*) was determined after oral exposure. Adult worker bees were exposed to

nominal doses of 0.0625, 0.125, 0.25, 0.50 and 1.0 µg a.i./bee dispersed in sucrose solution and observed for 48 hours. In addition, a sucrose solution control was tested. A dose-response effect on diet consumption was observed beginning at the lowest dose indicating sulfoxaflor was not palatable to the bees. There was 7% mortality in the control group with dose-response mortality ranging 27-100% in the treatment groups. One bee (3%) in each of the 0.125, 0.25 and 0.50 µg a.i./bee treatments exhibited sublethal effects (lying on back, lethargy) at the end of the test, for which death may have been imminent. The 48-hour LD_{50} was 0.146 µg a.i./bee. This study is classified as acceptable.

Vinall S (2009; MRID 47832107). The acute toxicity of the sulfoxaflor degradation product, X11719474 (purity 99.9 % w/w) to the honeybee (*Apis mellifera*) was determined after oral exposure. Adult worker bees were exposed in two separate tests to a nominal dose of 100 µg/bee (48-hour limit test) and nominal doses of 20, 40, 60, 80 and 100 µg/bee (96-hour dose-response test) dispersed in sucrose solution. In addition, a sucrose solution controls were tested. There was no effect on diet consumption in either test indicating X11719474 was palatable to the bees. In the 48-hour limit test, there was 4% mortality in the controls and 28% mortality in the 100 µg/bee treatment. In the 96-hour dose-response test, there was no treatment-related mortality. No sublethal effects were noted at the end of either test. Both 48-hour and 96-hour LD_{50} values were >100 µg/bee. This study is classified as acceptable.

Vinall (2010; MRID 48445809). The acute toxicity of the sulfoxaflor metabolite X11721061 (purity 99 % w/w) to the honeybee (*Apis mellifera*) was determined after oral exposure. Adult worker bees (approximately 2 weeks of age) were exposed to in a 48-h limit test to a nominal dose of 100 µg a.i./bee in a 50% sucrose solution distributed among 5 replicate cages containing 10 bees each. Results from a previous range finding test indicated the acute oral LD50 was > 100 µg a.i./bee . In addition, a sucrose solution controls were tested. No mortality occurred after 48 hours in both the control and treatment groups. Based on the amount of material consumed, the 48-hour LD_{50} value is >103.5 µg a.i./bee. No sublethal signs of toxicity were observed (e.g., lethargy, bees on back).

To confirm the sensitivity of the test insects, bees from the same hive were also tested with technical-grade dimethoate (dissolved in acetone and diluted with 50% w/v sugar solution) in a separate bioassay. The dimethoate was applied at a series of doses (nominally 0.20, 0.175, 0.15, 0.125 and 0.10 µg a.i./bee). Three replicate cages of 10 bees each (i.e. 30 bees per treatment in total) were used for each treatment and acetone diluted in 50% w/v sugar solution was used as a control. The acute oral LD_{50} for dimethoate is 0.16 (0.138-0.177) µg a.i./bee, which is within the historical range for this chemical (0.10 and 0.35 µg a.i./bee). This study is classified as acceptable.

Acute Oral Toxicity of Formulated Product to Adult Bees

Vinall (2009; MRID 47832417). The acute toxicity of GF-2032 (suspension concentrate, 22.0% w/w sulfoxaflor) to the honeybee (*Apis mellifera*) was determined after oral exposure. Adult worker bees were exposed to nominal doses of 0.0063, 0.0125, 0.025, 0.05, 0.1 and 0.2 µg a.i./bee dispersed in sucrose solution and observed for 48 hours. In addition, a sucrose solution control was tested. A slight effect on diet consumption beginning at 0.1 µg a.i./bee was observed indicating sulfoxaflor was not palatable to the bees. After 48 hours, there was no mortality in the control group and dose-response mortality was observed in the treatment groups ranging 2-96%. One bee (3%) in the 0.05 µg a.i./bee treatment exhibited sublethal effects (such as uncoordinated attempts to move, increased amounts of grooming, lethargy or diarrhea) at the end of the test. The 48-hour LD_{50} was 0.0515 µg a.i./bee. This study is classified as acceptable.

Vinall (2009; MRID 47832418). The acute toxicity of GF-2032 (suspension concentrate, 22% w/w sulfoxaflor) to the bumblebee (*Bombus terrestris*) was determined after oral exposure. Adult worker bees were exposed to nominal doses of 0.010, 0.019, 0.035, 0.065 and 0.120 µg a.i./bee dispersed in sucrose solution and observed for 72 hours. In addition, a sucrose solution control was tested. After 72 hours, there was 6.7% mortality in the control group and dose-response mortality was observed in the treatment groups ranging 10.0-96.7%. No sublethal effects were observed throughout the duration of the test. The 72-hour LD_{50} was 0.027 µg a.i./bee. This study is classified as supplemental (but acceptable for quantitative use in risk assessment) because bumblebee studies do not currently have an internationally accepted guideline; however, the 72-hour LD_{50} was determined to be reliable for regulatory purposes.

Oral Toxicity of TGAI To Larval Bees

Stempniewicz A (2012; MRID 48755602). This laboratory study was conducted based on the publication of Aupinel *et al.* 2009[1] to determine the effects of XDE-208 (active ingredient sulfoxaflor on the larval, pupal and adult emergence of the honeybee, *Apis mellifera carnica* L. This study included five treatment groups of the test item applied at concentrations of 0.0002, 0.002, 0.02, 0.2 and 2.0 µg a.i. in 30 µl diet/bee larvae. The control group was treated with 30 µl diet in purified water and the reference item (dimethoate) was applied at 5 µg a.i. in 30 µl diet/bee larvae. All treatment groups were treated once on day four of the experiment using a micropipette. Two test units (replicates) containing 30 first instar honeybee larvae were set up for each treatment. Larvae were fed once a day. On day four, treatments were applied to the culture plates that contained one larvae plus diet per cell. The culture plates were placed into a hermetic container that kept relative humidity at a mean of 90%. The container was then kept in a climate chamber at 33-35°C. On day 7, when pupation normally occurs, larvae mortality was assessed and the dead larvae was removed. On day 15, pupae mortality was assessed and dead pupae were removed. The remaining living pupae were then transferred to an emergence box that was again, kept in the hermetic container that was kept in a climate chamber. Adult bee emergence occurred from day 15 to 18. Mortality and rate of emergence were assessed on day 18. Mortality values were corrected using Abbott's formula (1925). LC_{10} and LC_{50} values were calculated with logistic regression using corrected mortality data from days 7 and 18.

In Aupinel *et al.* 2009, two validity criterions were set: control mortality must be lower than 15% at day 6; and successful hatch of adults in at least the control group. The validity criteria expressed in this trial included: larval mean control mortality should not be > 15% by day 7; and mean mortality of the reference item should be ≥ 50%. The mean mortality of larvae in the control treatments on day 7 was 8.3%. The mean mortality of the reference item (dimethoate) on day 18 was 100%. Both validity criterions were met.

A rate effect was evident across the range of doses tested. The LD_{50} for larvae by day 7 was greater than 2.0 µg a.i./bee larvae and the LD_{50} for total mortality (larvae + pupae) by day 18 was 0.22 µg a.i./bee larvae (0.08 – 0.35 CI). Because of the very high mortality observed in the control groups at 18 days, the 7-d LD_{50} is thought to be more reliable. The emergence rate on D18 was 50.0 %, 68.3 %, 70.0 %, 46.7 %, 35.0 %, 0.0 % in the control and the 0.0002, 0.002, 0.02, 0.2, 2.0 µg a.i. / bee larvae treatment groups, respectively. There were no morphological parameter differences recorded at any time, across any of

[1] Aupinel *et al*. 2009. Honey bee brood ring-test: method for testing pesticide toxicity on honeybee brood in laboratory conditions. In: Julius-Kühn-Archiv 423 (2009), Hazards of pesticides to bees -10th Int. Symp. of the ICP-BR Bee Protection Group, Bucharest (Romania), Oct 8-10, 2008.

the different honeybee lifestages. This study is classified as supplemental (the 7-D LD50 is considered acceptable for quantitative use in risk assessment).

Stempniewicz A (2012; MRID 48755603. This laboratory study was conducted based on the publication of Aupinel *et al.* 2009 to determine the effects of repeated doses of XDE-208 (active ingredient sulfoxaflor) on the larval, pupal and adult emergence of the honeybee, *Apis mellifera carnica* L. This study included five treatment groups of the test item applied at cumulative doses of 0.0001, 0.0002, 0.002, 0.02 and 0.2 µg a.i. XDE-208 / bee larvae in 20-50 µl diet/bee larvae. The control group was treated with 20-50 µl diet in purified water and the reference item (dimethoate) was applied at a cumulative dose of 5 µg a.i. in 20-50 µl diet/bee larvae. All treatment groups were treated once/day (except day 2) on days 1 through 6, consistent w/ the protocol of Aupinel *et al.* 2009.

Two test units (replicates) containing 30 first instar honeybee larvae were set up for each treatment. Larvae were fed once a day. On days 1, 3, 4, 5, and 6, treatments were applied to the culture plates that contained one larvae plus diet per cell. The culture plates were placed into a hermetic container that kept relative humidity at a mean of 93%. The container was then kept in a climate chamber at 33-35°C. On day 7, when pupation normally occurs, larvae mortality was assessed and the dead larvae was removed. On day 15, pupae mortality was assessed and dead pupae were removed. The remaining living pupae were then transferred to an emergence box that was again, kept in the hermetic container that was kept in a climate chamber. Adult bee emergence occurred from day 15 to 18. Mortality and rate of emergence were assessed on day 18. Mortality values were corrected using Abbott's formula (1925). LD_{10} and LD_{50} values were calculated with logistic regression using corrected mortality from days 7 and 18.

In Aupinel *et al.* 2009, two validity criterions were set: control mortality must be lower than 15% at day 6; and successful hatch of adults in at least the control group. The validity criteria expressed in this trial included: larval mean control mortality should not be > 15% by day 7; and mean mortality of the reference item should be ≥ 50%. The mean mortality of larvae in the control treatments on day 7 was 5%. The mean mortality of the reference item (dimethoate) on day 18 was 100%. Both validity criteria were met.

Mean control mortality by day 7 was low (5%) while that by day 15 and 18 was high (38.3% and 58.3%). Furthermore, mean emergence in controls by day 18 was relatively low (42%). Results from Aupinel *et al.* 2007[2] indicate mean adult emergence in controls of 70% or higher. Therefore, results from day 7 are considered most applicable to risk assessment purposes. At and below a cumulative 6 day dose of 0.02 µg a.i./bee, larval mortality ranged from 8.3 to 15% with no obvious dose-response relationship by day 7. At 0.2 µg a.i./bee, 45% mortality occurred on day 7. The 7 day LD_{10} = 0.085 µg a.i./bee larvae (CI = 0.005 – 1.49) and the 7 day LD_{50} was greater than 0.2 µg a.i./bee larvae. The emergence rate was 41.7 %, 38.3 %, 41.7 %, 20.0 %, 38.3 %, 0.0 % and 0.0 % for the control and the 0.0001, 0.0002, 0.002, 0.02, 0.2 µg a.i. / bee larvae treatment groups, respectively. There were no morphological parameter differences recorded at any time, across any of the different honeybee lifestages. This study is classified as supplemental (the 7-D LD50 is considered acceptable for quantitative use in risk assessment).

[2] Aupinel et al. 2007. Toxicity of dimethoate and fenoxycarb to honey bee brood (*Apis mellifera*), using a new *in vitro* standardized feeding method. *Pest. Manag. Sci*. 63:1090-1094.

Acute Foliar Residue Toxicity

Bergfield (2009; MRID 47832512). The effects of foliar residues of GF-2372 (water-dispersible granule, 50% w/w sulfoxaflor) on the honeybee (*Apis mellifera*) were determined after 24 hours of contact exposure. Alfalfa foliage was sprayed at nominal rates of 100 and 200 g a.i./ha. Residues were allowed to weather in the field for 3, 6 and 24 hours of application. In addition, untreated alfalfa foliage was maintained for the controls. The alfalfa was harvested and placed into cages containing the bees. After 24 hours, mean mortality in the controls was 5%. In the 3-, 6-, and 24-hour weathered treatments, the corrected mean mortalities were 0.7, 2.8 and 14% at 100 g a.i./ha and 9.9, 9.9 and 15% at 200 g a.i./ha. Sublethal symptoms were not observed in the surviving bees. This study is classified as acceptable.

Lee (2008 MRID 47832420). The effects of foliar residues of GF-2032 (suspension concentrate, 22% w/w sulfoxaflor) on the honeybee (*Apis mellifera*) were determined after 24 hours of contact exposure. Alfalfa foliage was sprayed at a nominal rate of 200 g a.i./ha. Residues were allowed to weather in the field for 3, 6 and 24 hours of application. In addition, untreated alfalfa foliage was maintained for the controls. The alfalfa was harvested and placed into cages containing the bees. After 24 hours, mean mortality in the controls was 0.7%. In the 200 g a.i./ha treatments weathered for 3, 6 and 24 hours, the corrected mean mortalities were 4.7, 2.0 and 1.3%, respectively. Sublethal symptoms in the surviving bees included bees lying on their back and lethargy. This study is classified as acceptable.

II. Semi-Field Tunnel Studies

1. Hecht-Rost (2009; MRID 48445806). This semi-field tunnel study was conducted to determine the effects of GF-2032 (nominally a 240 g a.i./L SC formulation containing the insecticide sulfoxaflor on the honeybee, *Apis mellifera carnica* L. This study included five treatment groups of the test item GF2032 applied at calculated rates of 99, 50, 24, 13.6 and 6.5 g a.i./ha in separated tunnels. A sixth group (tunnel) treated with tap water served as control. As reference item "Perfekthion" BAS 152 11 I (dimethoate) was applied at a rate of 400 g ai/ha (nominal). All applications were conducted when bees were actively foraging (> 5 bees/m^2) during daily bee-flight and with a spay volume of 300 L water/ha. The effect of the test item was examined on small bee colonies in tunnels (approx. 100 m^2) placed on plots with *Phacelia tanacetifolia.*

Mortality, behavior, flight intensity, condition of the colonies and the development of the bee brood (% comb area with eggs, larvae, and capped brood) were assessed prior to application and up to 7 days after the application. In order to evaluate the magnitude of residues of the test item GF-2032 pollen samples from inside the hives and flowers of *P. tanacetifolia* were taken for analysis.

Adult Mortality and Flight Intensity. Application of sulfoxaflor up to 99 g ai/ha appeared to increase bee mortality by up to 7X compared to controls during the first 3 days after application. After this time, bee mortality returned to levels observed in the controls. An approximate dose-dependent decline in flight intensity was also observed from 0DAA through 3DAA in the sulfoxaflor treatments. Flight intensity was reduced in sulfoxaflor treatments relative to controls from 4DAA through 7DAA, although dose-dependency was not observed. Mortality in the reference toxicant (dimethoate) treatment was elevated by up to 10X of controls from 0DAA to 3DAA, indicating that the application procedures resulted in significant exposure to bees. Similarly, flight intensity was extremely impacted (reduced) in the dimethoate treatment.

Colony Strength. The effect of sulfoxaflor on colony strength is difficult to interpret due to the large difference among control and treated hives prior to pesticide application (# bees/hive in controls was 2X that of treated hives on -2DAA). On 7DAA, no obvious dose-dependent trend in colony strength was apparent among hives from plots treated with 6.5 to 99 g ai/ha sulfoxaflor. The effects of sulfoxaflor on bee brood are considered inconclusive due to the presence of *Varroa* mites in control hives and the short observation period (7 days).

Residues. Residues of sulfoxaflor up to 1 ppm were detected in *Phacelia* pollen 7 days after application and showed a general decline with application rate. Residues in flowers (max of 1.7 ppm on 0DAA) declined steadily in the T3/24 g ai/ha treated plots to about 0.1 ppm by 7DAA. Based on this decline, one can infer higher residues in pollen on 0DAA.

Conclusions. Although this study had several strengths (multiple dosing levels, measurement of residues, documented exposure and effects with reference toxicant (dimethoate), it also had several limitations that either confounded the interpretation of results and/or limits there use in pollinator risk assessment. Specifically, the maximum application rate tested (99 g ai/ha) was ont third the proposed seasonal maximum on the US label (300 g ai/ha). The presence of *Varroa* mites in control hives may have compromised control brood performance measures (no *Varroa* were reported in other treatments). Furthermore, the post treatment observation was only 7 days which may be insufficient to detect effects on developing brood. For brood development, OECD Guideline 75 suggests 7 d exposure + 19 d observation period.

2. Schmitzer (2010; MRID 48445807). Tunnels (14 m length x 5.5 m width x 2.5 m height) were set up on a *ca.* 40 m^2 plot of *Phacelia tanacetifolia* (4m x 10m) and small bee colonies were introduced eight days before the daytime application. A water control and a toxic reference and Perfection EC [400g/L dimethoate]) were included in the study. Three application scenarios were conducted:

- Scenario 1: 48 g a.i./ha of GF-2032 was applied to the crop in the evening after bee flight to evaluate the impact of dried residues on foliage. The day after following this application, the bees were introduced to the tunnels and were exposed to the residues of the test item for 9 days.
- Scenario 2: 24 g a.i./ha of GF-2032 was applied during the day with bees actively foraging.
- Scenario 3: 48 g a.i./ha of GF-2032 was applied in the middle of the day with bees actively foraging.

The water-treated control and reference item (600 g dimethoate/ha) were applied to the whole plot in two operations, in the middle of the day with foraging bees present (daytime applications). The trial was carried out using three tunnels *(i.e.* replicates) for each treatment group, with one bee hive per tunnel. Mortality, foraging activity and behavior of adult bees were recorded daily over the course of the study. Brood condition was assessed 4 days prior to application and 9 days following application.

Adult Mortality. Adult foraging bees exposed to GF-2032 at rates of 24 and 48 g a.i./ha (during flight) exhibited a statistically-significant increases in mortality of up to 20X the rate observed in controls on the day of application. This increase in mean daily worker bee mortality was short lived, however, having returned to a factor of 1.5X of controls by 1DAA (for the 24 g a.i./ha during flight; 48 g a.i./ha after flight treatments) and 3DAA(for the 48 g a.i./ha during flight treatment). No statistically significant effects on daily mortality rates were detected after 0DAA or when data were combined from 0DAA and 7DAA. The lack of statistical significance should be interpreted with caution because of the apparent low statistical power of the test for this endpoint.

Foraging Intensity. Application of GF-2032 led to a reduction of foraging activity of bees on the day of application. Relative to control bees, mean foraging intensity on 0DAA was reduced by 25% in the 24 g a.i./ha (during flight) and 48 g a.i./ha (after flight) treatments and was reduced by 50% in the 48 g a.i./ha treatment. No statistical analysis was conducted on the 0DAA results. For the remainder of the test, mean forage intensity of bees was comparable between the controls and GF-2032 treatments, indicating the reduction in foraging intensity was a short-term effect. When forage intensity was evaluated from 0DAA through 7DAA, no statistically significant differences were detected according to the study author. Foraging activity in the dimethoate-treated tunnels (reference item) was severely reduced from 0DAA through 7DAA, which indicates the methods used to quantify foraging activity were appropriately sensitive.

Behavioral Effects. As seen with bee mortality and flight intensity results, the behavioral abnormalities reported for adult worker bees were short lived, having occurred only on 0DAA for the 48 g a.i./ha (after flight) and 24 g a.i./ha (during flight) treatments and 0DAA through 1DAA for the 48 g a.i./ha (during flight) treatment. Behavioral abnormalities included uncoordinated movement, cramps, intensive cleaning and aggressiveness.

Brood Condition. The condition of brood among the hives was similar 4 days prior to pesticide application, which indicates differences in brood condition among hives would not likely confound interpretation of the study results. Nine days following the applications, all brood stages could be found at the end of the test in each of the colonies. The presence of nectar and pollen in the combs on 9DAA indicates that bees were able to forage successfully on the crop. The mean % comb area with nectar, pollen, eggs and larvae were comparable among treatments and controls, although no statistical analysis was conducted of these data. The only noticeable difference among brood condition was a slight increase in the percent capped brood in treatments (20-40%) compared to controls (20-25%). Given the small magnitude of increase and the high variability within treatments, this difference is not expected to be statistically significant and its biological significance is uncertain.

Conclusions. This study had a number of strengths including:

- A number of exposure scenarios were used (*e.g.*, exposure to aged residues and direct exposure to daytime applications which simulate actual use conditions of the product).
- Replicated treatments were used which permitted statistical analysis of the data.
- Colony attributes were similar across treatments prior to test initiation
- The reference toxicant treatment demonstrated that the application methods used documented sufficient exposure to foraging bees.

However, this study also has some significant limitations including:

- The application rates tested (24 and 48 g a.i./ha) were below the maximum single and annual application rates proposed for registration in the US (*e.g.*, 2 x 150 g a.i./ha for cotton).
- Colonies were not evaluated subsequent to the 9-day tunnel exposures; therefore, longer-term effects of the treatments on colony and brood condition could not be evaluated.
- Colonies were introduced into tunnels 8 days prior to pesticide application, which is greater than the 2-3 days recommended in the test guideline. Confinement in tunnels is known to adversely affect honeybees and should be minimized.

- No assessment of overall colony strength (numbers of bees) was reported at test initiation or termination. Such information would have provided context to the number of worker bees killed by the test product and reference toxicant.
- Statistical analysis was used to analyse the data however large differences were required in the means between the treatment and control groups in order to detect a statistically significant difference. For example, for the 48 g a.i./ha application after bee flight, the mean number of dead bees per day on 0DAA 164.3 (SD=28.0) and was found not to be significantly different from the control dead bee rate of 26.7 (SD=12.1). This reflects the high variability in this measurement endpoint within treatments and the low statistical power. Additional replicates would be needed to improve statistical power of this study.

3. Schmitzer (2011a; 48755604). The effects of the test item on small bee colonies were examined in tunnels (14 m length x 5.5 m width x 2.5 m height) placed on plots of *Phacelia tanacetifolia*. The study included a water control and a toxic reference (Insegar [250 g/kg fenoxycarb]). Three application scenarios were conducted:

- **Scenario 1:** 48 g a.i./ha of GF-2626 was applied to the crop before flowering. Nine days following this application, the bees were introduced to the tunnels when the *Phacelia* was now in full flower and were exposed to the residues of the test item. This application was conducted 13 day before the daytime applications.
- **Scenario 2:** In the evening before the daytime application two test item rates of 24 and 48 g a.i./ha were applied after the bees were active in order to expose the bees to dried residues of the test item the next day.
- **Scenario 3:** 24 g a.i./ha of GF-2626 was applied in the middle of the day with foraging bees present (daytime applications).

The water-treated control and the reference item (300 g fenoxycarb/ha) were applied also during daytime with foraging bees present. The trial was carried out using three tunnels *(i.e.* replicates) for each treatment group, with one bee hive per tunnel. Following the daytime applications, ontogenesis of a defined number of honey bee eggs was observed for each treatment group and colony. Mortality of adult bees and pupae as well as foraging activity of the adult bees was also assessed. The condition of the colonies was assessed in regular intervals until the end of the trial.

The exposure period of the bees to the water, test item and reference item treated crops in the tunnels was 7 days (10 days for the pre-flower treatment). Afterwards the bee hives were removed from the tunnels to an area with no main flowering, bee attractive crops. Ontogenesis of the bees from egg to adult workers was observed for a period of 22 days. This was done by marking 120 eggs at the first brood area fixing day BFDO (BFD = Brood Area Fixing Day) and investigating the further progress of their development in regular intervals until day 21 following the daytime application (BFD 22 following BFDO).

Adult and Pupae Mortality. Adult foraging bees exposed to pre-flower treatment with 48 g a.i./ha sulfoxaflor, to dried residues applied at 24 and 48 g a.i./ha after bee flight and to direct exposure to 24 g a.i./ha had no statistically significant mortality compared to the control over the 7 day exposure period and up to 27 days following application. The results should be interpreted with caution because of the statistical power of the test. The mean mortality was higher in all of the treatment groups compared to the control for the entire 27 day observation period. Pupae exposed to pre-flower treatment with 48 g a.i./ha sulfoxaflor, to dried residues applied at 24 and 48 g a.i./ha after bee flight and to direct exposure to 24 g a.i./ha had no statistically significant effects compared to

the control over the 7 day exposure period and up to 27 days following application. Very few dead pupae were found in the control or in any of the treatments over the period of the test.

Foraging Activity. Foraging activity of bees exposed to pre-flower treatment with 48 g a.i./ha sulfoxaflor, to dried residues applied at 24 g a.i./ha after bee flight and to direct exposure to 24 g a.i./ha had no statistically significant effects compared to the control over the 7 day exposure period. Foraging activity was, however statistically significantly reduced in the 48 g a.i./ha application after bee flight compared to the control over the 7 day exposure period. The results should be interpreted with caution because of the statistical power of the test. The mean foraging activity was lower in all of the treatment groups compared to the control for the 7 day exposure period.

Brood and Colony Development. There was a similar pattern of colony development in the control and the test item treatment groups 24 and 48 g a.i./ha after bee flight and 24 g a.i./ha during bee flight. Colony sizes remain on a comparable level until day +27 ranging around 57 to 129 % compared to the initial values. Colony sizes in the 48 g a.i./ha pre-flowering treatment group was somewhat lower compared to the other colonies (with and without the exclusion of the colony which was temporarily queenless).

The effects of sulfoxaflor on bee brood are considered inconclusive due to the fact that the mean brood termination rate was 56.4% in the control which appears unusually high. Notably, Schur *et al.* (2003)[3] reported that brood termination rate in control hives varied from 8% to 43% in a ring-test of five trials of the OECD 75 tunnel study design. Importantly, they attributed the high brood termination rates (32-43%) in three trials to poor weather conditions that occurred during the studies. In a recent review of historical control data for brood termination rate, Pistorius *et al*[4]*.* correlated increases in control brood termination rate with season of test initiation and available forage area. Regardless of the source of the high brood termination rate in the control treatments of this study, it likely reflects some stress on the bees caused by the study design and creates substantial uncertainty as to the ability of the study to detect the effects of sulfoxaflor on developing brood.

Application of the reference item Insegar (300 g fenoxycarb/ha) resulted in high numbers of dead pupae after application, which was statistically significant different from the control for the period day 8 after application to day 27 (529 dead pupae) and from day 0 to day 27 (531 dead pupae). Colonies in the reference item treatment group developed normal until day +15 but thereafter decreased down to < 50 % at the last assessment, compared to the initial value.

Conclusions. This study had several strengths including the use of a number of exposure scenarios e.g., exposure to aged residues and direct exposure to daytime applications which simulate actual use conditions of the product, replicated treatments which permit statistical analysis, and exposure to bee brood was confirmed because of recorded mortality of pupae with the reference toxicant (fenoxycarb) which is an insect growth regulator.

The study also had several limitations that confounded the interpretation of results and/or limits their use in a pollinator risk assessment including:

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3 Schur, A., *et al.* 2003. Honey bee brood ring-test in 2002: method for the assessment of side effects of plant protection products on the honey bee brood under semi-field conditions. *Bull. Insectol.* 56(1):91-96.
4 Pistorius, J. *et al.* 2011. Effectiveness of method improvements to reduce variability of brood termination rate in honeybee brood studies under semi-field conditions. *International Commission For Plant-Bee Relationships Bee Protection Group 11th International Symposium Hazards Of Pesticides To Bees.* Wageningen, The Netherlands, November 2-4, 2011.

- The application rates tested (24 and 48 g a.i./ha) were below the maximum single airblast application rates proposed for registration in the US (e.g., 2 x 150 g ai/ha for stone fruit).
- The mean brood termination rate was 56.4% in the control which seems unusually high, which makes any conclusions regarding the development of the brood in the treatment groups difficult to interpret. Although no specific guidance is available regarding brood termination rate in controls, it is generally thought that more than 25% brood termination rate in controls in unacceptable.
- Statistical analysis was used to analyse the data however large differences were required in the means between the treatment and control groups in order to detect a statistically significant difference. For example, for the evening application of 24 and 48 g a.i./ha the day following application a mean of 24.3 and 24.7 dead bees were found in both treatment groups (9.7 in the control group), which was not statistically significant for both treatment groups. This due to the statistical power of the analysis used.

4. Schmitzer (2011b; 48755605). Tunnels (14 m length x 5.5 m width x 2.5 m height) were set up on a *ca.* 50 m^2 plot of *Phacelia tanacetifolia* (2 x 24 m^2) and small bee colonies were introduced ten days before daytime applications. A water control and two toxic references (Insegar [250 g/kg fenoxycarb] and Perfection EC [400g/L dimethoate]) were included in the study. Three application scenarios were conducted:

- **Scenario 1:** 48 g a.i./ha of GF-2626 was applied to the crop before flowering. Five days following this application, the bees were introduced to the tunnels and were exposed to the residues of the test item. This application was conducted 15 days before the daytime applications.
- **Scenario 2**: In the evening before the daytime application 24 g a.i./ha was applied after the bees were active in order to expose the bees to dried residues of the test item the next day.
- **Scenario 3:** 24 g a.i./ha of GF-2626 was applied in the middle of the day with foraging bees present (daytime applications). The water-treated control and both reference items (300 g fenoxycarb/ha and 600 g dimethoate/ha) were applied to the whole plot in two operations, in the middle of the day with foraging bees present (daytime applications).

The trial was carried out using three tunnels *(i.e.* replicates) for each treatment group, with one bee hive per tunnel. Following the daytime applications, ontogenesis of a defined number of honey bee eggs was observed for each treatment group and colony. Mortality of adult bees and pupae as well as foraging activity of the adult bees was also assessed. The condition of the colonies was assessed in regular intervals until the end of the trial.

The exposure period of the bees to the water, test item and reference item treated crops in the tunnels was 7 days (17 days for the pre-flower treatment). Afterwards the bee hives were removed from the tunnels to an area with no main flowering, bee attractive crops. Ontogenesis of the bees from egg to adult workers was observed for a period of 21 days. This was done by marking 120 eggs at the first brood area fixing day BFDO (BFD = Brood Area Fixing Day) and investigating the further progress of their development in regular intervals until day 20 following the daytime application (BFD 21 following BFDO).

Adult and Pupae Mortality. Adult foraging bees exposed to pre-flower treatment with 48 g a.i./ha sulfoxaflor, to dried residues applied at 24 g a.i./ha after bee flight and to direct exposure to 24 g a.i./ha had no statistically significant effects compared to the control over the 7 day exposure period and up to 27 days following application. The results should be interpreted with caution because of the statistical

power of the test. Specifically, on day 0 in both 24 g a.i./ha treatments, a 3-fold increase in mortality occurred but this was not statistically significant. By day 1 after application, mortality returned to levels comparable to controls. The mean mortality was slightly higher in all of the treatment groups compared to the control for the entire 27 day observation period, although differences were not statistically significant. Pupae exposed to pre-flower treatment with 48 g a.i./ha sulfoxaflor and to direct exposure to 24 g a.i./ha had no statistically significant effects compared to the control over the 7 day exposure period and up to 27 days following application. A high number of dead pupae (71) were observed in the 24 g a.i./ha treatment group after bee flight which was statistically significant compared to the control. This pupae mortality, however, was limited almost entirely to one hive and it is therefore unclear if this is treatment related.

Application of the reference item Insegar (300 g fenoxycarb/ha) resulted in high numbers of dead pupae after application, which was statistically significant different from the control for the period day 8 after application to day 27 (97 dead pupae) and from day 0 to day 27 (117 dead pupae). Only 1 dead pupa was found following the application with the reference item Perfekthion (600 g dimethoate/ha).

Foraging Activity. Foraging activity of bees exposed to pre-flower treatment with 48 g a.i./ha sulfoxaflor, to dried residues applied at 24 g a.i./ha after bee flight and to direct exposure to 24 g a.i./ha had no statistically significant effects compared to the control over the 7 day exposure period. The results should be interpreted with caution because of the statistical power of the test. The mean foraging activity was lower in all of the treatment groups compared to the control for the 7 day exposure period.

Colony and Brood Development. Colony sizes among all treatment groups did not differ very much in size over the course of the study. Only at the last assessment on day 60, was there a clear decrease. There was a similar pattern of development in the control and all test item treatment groups. Colony sizes remain on a comparable level until day +27 ranging around 81 to 131 % compared to the initial values. At the last assessment period (day +60) all test items and control colonies ranged from 69 % to 81 % compared to their initial values. Colonies in the reference item treatment group with Insegar showed a progress until day 16 and thereafter decreased. Reference item Perfekthion EC led to a continuous decrease of number of bees in the treated colonies until test end on day 60

The effects of sulfoxaflor on bee brood are considered inconclusive due to the fact that the mean brood termination rate was 65.3% in the control which appears unusually high. Notably, Schur *et al.* (2003)[5] reported that brood termination rate in control hives varied from 8% to 43% in a ring-test of five trials of the OECD 75 tunnel study design. Importantly, they attributed the high brood termination rates (32-43%) in three trials to poor weather conditions that occurred during the studies. In a recent review of historical control data for brood termination rate, Pistorius *et al*[6]. correlated increases in control brood termination rate with season of test initiation and available forage area. Regardless of the source of the high brood termination rate in the control treatments of this study, it likely reflects some stress on the bees caused by the study design and creates

5 Schur, A., *et al.* 2003. Honey bee brood ring-test in 2002: method for the assessment of side effects of plant protection products on the honey bee brood under semi-field conditions. *Bull. Insectol.* 56(1):91-96.
6 Pistorius, J. *et al.* 2011. Effectiveness of method improvements to reduce variability of brood termination rate in honeybee brood studies under semi-field conditions. *International Commission For Plant-Bee Relationships Bee Protection Group 11th International Symposium Hazards Of Pesticides To Bees.* Wageningen, The Netherlands, November 2-4, 2011.

substantial uncertainty as to the ability of the study to detect the effects of sulfoxaflor on developing brood

Conclusions. This study had several strengths including 1) the use of a number of exposure scenarios *e.g.*, exposure to aged residues and direct exposure to daytime applications which simulate actual use conditions of the product, 2) replicated treatments which permit statistical analysis, and 3) exposure to bee brood and adults was confirmed because of recorded mortality of pupae and adults with the reference toxicants fenoxycarb and dimethoate, respectively.

The study also had several limitations that confounded the interpretation of results and/or limits their use in a pollinator risk assessment including:

- The application rates tested (24 and 48 g a.i./ha) were below the maximum single airblast application rates registered in Canada for pome fruits, grapes, stone fruits and tree nuts and below the maximum seasonal application rates for all registered uses in Canada with the exception of succulent and edible podded beans and dry beans. The rates used in this study are also below maximum single rates proposed for registration in the United States (*e.g.*, 100 g ai/ha for cotton).
- The mean brood termination rate was 65.3% in the control which seems unusually high, which makes any conclusions regarding the development of the brood in the treatment groups difficult to interpret.
- Statistical analysis was used to analyse the data however large differences were required in the means between the treatment and control groups in order to detect a statistically significant difference. For example, for the evening application of 24 g a.i./ha on day 0 following the evening application a mean of 81.7 dead bees was found in the treatment group compared to 26.7 mean dead bees in the water control group. This was not statistically significant. This is due to the lack of statistical power of the analysis used. Additional replicates for the treatment groups would be required to increase the statistical power of the test.

5. Schmitzer (2011c). This study was conducted to determine the effects on foraging bees due to direct exposure (application during bee activity) on flowering crops at 4, 8 and 24 g a.i./ha of GF-2626. The control group (water) and two reference item groups (thiamethoxam or dimethoate, respectively) were treated also during bee flight. Tunnels (14 m length x 5.5 m width x 2.5 m height) were set up on a 40 m^2 plot of flowering *Phacelia tanacetifolia* (2 x 20 m^2) and small bee colonies were introduced 8 days before the applications. One bee hive was used per tunnel.

Small colonies of honey bees *(Apis mellifera* carnica L.) were maintained according to normal beekeeping practice, containing 4 honeycombs each. The preliminary brood check indicated healthy colonies with a present queen. Due to the late season in which the study was conducted (October in Germany), not all brood stages could be found. The study authors indicated that either a queen or a sufficient amount of eggs were found indicating that the colonies were queen-right. The mean number of bees per colony in the test groups three days before the application was similar.

The trial was performed using three tunnels for the different test item treatments (3 replicates/treatment), the control and both reference item treatments, respectively (total = 15 tunnels). The exposure phase of the bees to the treated crop was 7 days following the daytime applications. The conditions of the colonies were examined until 3 months following the initial applications. Mortality and foraging activity of the bees were assessed before and after application. Sublethal effects, such as changes in behavior, were also monitored. Condition of the colonies (food stores, brood status and

colony strength) was assessed 3 days before, 7 and 14 day after the application. 32 day and 3 months following the application the condition of the colonies was examined concerning the overall survival.

Mortality. Application of GF-2626 at rates of 4, 8 and 24 g ai/ha resulted in an increase in mean number of dead bees/colony relative to controls on the day of application (1.5X to 4X higher), although these increases were not statistically significant. From 1DAA through 7DAA, results between the control and GF-2626 treated hives were similar, indicating a transient effect of sulfoxaflor on bee mortality. Application of dimethoate and thiamethoxam (reference toxicants) resulted in much greater mortality compared to controls (40X) and for a longer period of time.

Foraging Activity. Similar to mortality, application of GF-2626 at rates of 4, 8 and 24 g ai/ha resulted in a reduction in foraging activity of bees on the day of application by 30-40% relative to controls. However, foraging activity in subsequent days recovered to levels that were similar or exceeded slightly those of controls. Application of the dimethoate and thiamethoxam reference toxicants resulted in a sustained (and statistically significant) depression of foraging activity which indicates the study design is able to detect effects on this endpoint.

Behavioral Abnormalities. As seen with bee mortality and flight intensity results, the behavioral abnormalities reported for adult worker bees were short lived, having occurred only on 0DAA for the 24 g a.i./ha treatment and up to 2DAA in the reference toxicant treatments.

Brood Development and Colony Strength. Due to the confounding influence of the late season and declining colony condition, the effect of GF-2626 or the reference toxicants on brood condition and colony strength are not considered valid as measured in this study. The late season at which the study was conducted resulted in severely depleted brood stock which likely confounded the ability to detect treatment related effects on brood condition.

6. Ythier 2012 MRID 48755606. GF-2372 (Batch No. E3461-80, content of sulfoxaflor 49.1 % w/w) was diluted in water and applied with a spray application to protected cotton at full bloom, at the following rates: 0.045 lb a.i./acre (1 or 2 applications at 5-day interval), 0.089 lb a.i./acre (2 applications at 5 day-interval) and 0.134 lb a.i./acre (2 applications at 5-day interval). When spray residues were dry, honey bee colonies were exposed to the treated crop in tunnels (two bee hives per tunnel) for 10 days. Samples of pollen (extracted from flowers), forager honeybees (for subsequent extraction of pollen loads and nectar) and pollen and larvae from the combs were taken and analyzed for sulfoxaflor (XDE-208) and its major metabolite X11719474. General conditions and weight of the colonies were recorded before and after exposure during the experimental phase, to ensure the colonies were in a suitable condition to fulfill the purpose of the experiment.

Assessment of the colonies (three days before first exposure to the test item = 3DBE) indicated that the test colonies were in a suitable condition to fulfill the purpose of the experiment (adequately fed, healthy and queen-right colonies, with at least 10,000 young honey bees, 4-5 combs of brood with all brood instars present and 2-3 combs of nectar and pollen).

- In pollen from plants, results ranged from below the LOD (0.01 ug/g) to 6.6560 µg/g for XDE-208 and from below the LOD (0.01 ug/g) to 0.0176 µg/g for X11719474.
- In pollen from bees, results ranged from 0.0126 to 2.780 µg/g for XDE-208 and from below the LOD to 0.0650 µg/g for X11719474.

- In nectar from bees, results ranged from below the LOD to 1.010 µg/g for XDE-208 and from below the LOD to 0.0210 µg/g for X11719474.
- In pollen from combs, results ranged from below the LOD to 1.190 µg/g for XDE-208 and from below the LOD to 0.0637 µg/g for X11719474.
- In larvae from combs, results ranged from below the LOD to 0.0815 µg/g for XDE-208 and from below the LOD to 0.0752 µg/g for X11719474.

Biological measurements of hive attributes indicated that foragers were able to obtain sufficient nectar to maintain the number of foragers in hives following 10 days exposure in tunnels treated with sulfoxaflor. However, pollen reserves were exhausted in all treatments by 10DAE, indicating the quantity and/or quality of cotton pollen was insufficient to maintain pollen stores. This apparent lack of pollen likely influenced the reduction in brood condition on 10DAE and 17DAE relative to 3DBE. Lack of a concurrent control precluded evaluation of sulfoxaflor effects separate from those which may have been caused by the tunnel enclosure environment.

Colony strength (total numbers of bees) was similar between the pre- and post application measurements within and among all treatments . This implies that conditions of the sulfoxaflor treatments did not result in an obvious decline in mean colony strength by 17DAFA, even at the maximum US application rate of 2 x 0.134 lb ai/A. Although lack of a current control and limited observation period precludes definitive conclusions regarding the effect of sulfoxaflor on colony strength in this study, these results suggest that major impacts on honey bee colony strength are not apparent with sulfoxaflor applications at the maximum US application rate, at least over the short term (*e.g.,* 17DAFA).

III. Sulfoxaflor Residue Studies

Cotton Residue Study (MRID 48755606). GF-2372 (sulfoxaflor 49.1 % w/w) was diluted in water and applied with a spray application to protected cotton at full bloom in a series of tunnel enclosures. Application rates include: 0.045 lb a.i./acre (1 or 2 applications at 5-day interval), 0.089 lb a.i./acre (2 applications at a 5-day interval) and 0.134 lb a.i./acre (2 applications at 5-day interval). When spray residues were dry, honey bee colonies were exposed to the treated crop in tunnels (two bee hives per tunnel) for 10 days. Samples of pollen (extracted from flowers), forager honeybees (for subsequent extraction of pollen loads and nectar) and pollen and larvae from the combs were taken and analyzed for sulfoxaflor and its major metabolite X474 on Day 0 after application (0DAA) through 10DAA. General conditions and weight of the colonies were recorded before and after exposure during the experimental phase, to ensure the colonies were in a suitable condition to fulfill the purpose of the experiment.

Assessment of the colonies (three days before first exposure to the test item = 3DBE) indicated that the test colonies were in a suitable condition to fulfill the purpose of the experiment (adequately fed, healthy and queen-right colonies, with at least 10,000 young honey bees, 4-5 combs of brood with all brood instars present and 2-3 combs of nectar and pollen).

A summary of reported residue values in various matrices from the cotton study is shown in **Table D-1.** One notable aspect of this study is how the biology of the cotton plant affects interpretation of the residue measurements made over time. Specifically, cotton flowers are known to remain open for approximately one day or less. Furthermore, at the relatively at high temperatures associated with the conduct of this study, pollen was noted to degrade relatively quickly in the flower (generally by mid-day to early afternoon). Thus, on days following sulfoxaflor applications, bees would not be able to forage

on flowers which were previously open during pesticide applications because flowers would not remain open beyond the day of pesticide application. It is therefore concluded that residues measured on the first application day reflect sulfoxaflor that has deposited onto pollen and nectar immediately after application. On days 1-4 and 6-10, residues in pollen and nectar are considered to reflect systemically transported chemical, since these sampled flowers were not open during the day of application. Pollen and nectar residues measured on DAA5 reflect both deposited and systemically transported chemical. An illustration of this interpretation of the sulfoxaflor residues in forager bee-collected pollen and nectar is shown in **Figure D-1 and D-2.**

Table D-1. Sulfoxaflor residues in pollen collected from cotton plants, pollen collected from foragers, and nectar collected from foragers (MRID 48755606)

Application Rate (lb ai/A)	Application Days		Non-Application Days (D1-D4 & D6-D10)	
	D0	D5	Min	Max
Pollen & Stamen from Plants (ppb)				
0.045 x 1	1,263	n/a	<10	<10
0.045 x 2	1,077	2,540	<10	61.3
0.089 x 2	6,656	691	<10	56.7
0.134 x 2	2,612	74.8	12.9	69.5
Pollen from Foragers (ppb)				
0.045 x 1	127 - 187	n/a	12.6	222
0.045 x 2	173 - 226	192 – 830	32.3	296
0.089 x 2	512 - 2,782	787 - 1,146	99.5	2,262
0.134 x 2	1,209 - 2,218	1,150 – 1,420	129	2,226
Nectar from Foragers (ppb)				
0.045 x 1	21.7 – 32.7	n/a	<10	126
0.045 x 2	<10	45.0 – 49.0	<10	42.0
0.089 x 2	<10 – 73.8	21.9 – 22.9	<10	35.5
0.134 x 2	51.7 – 109	21.9 – 43.7	<10	1,006

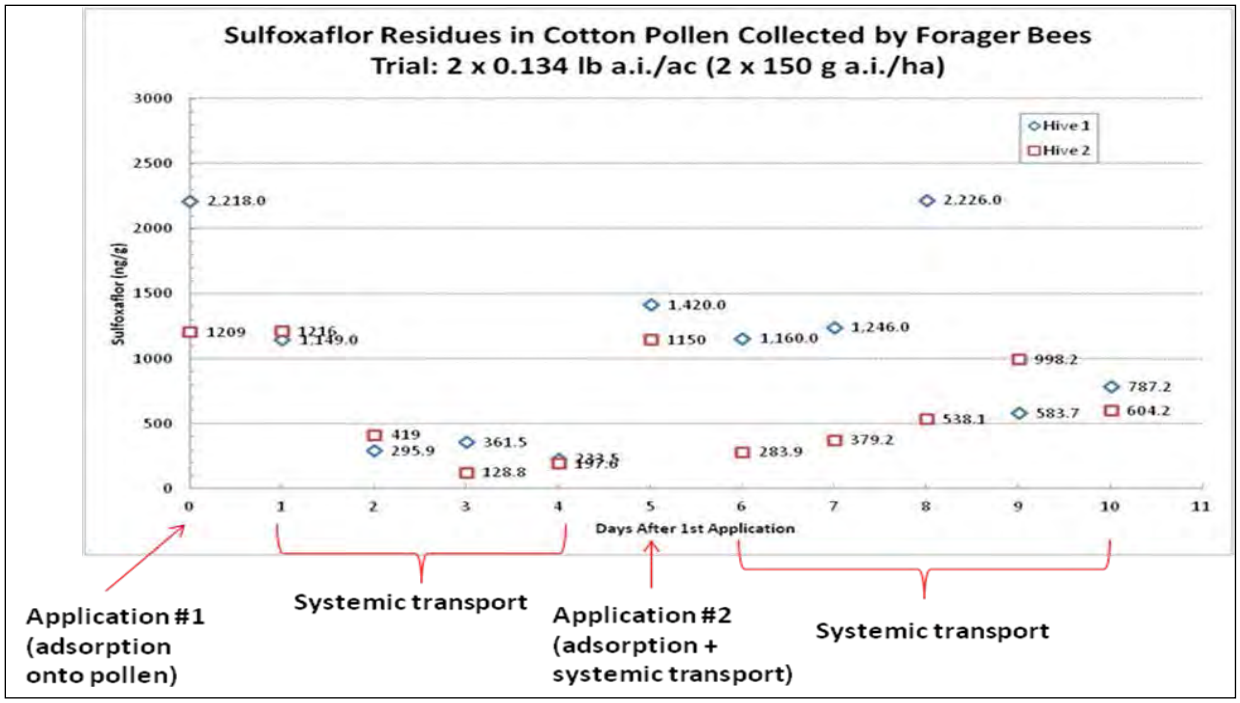

Figure D-1. Sulfoxaflor residues reported in pollen collected by forager bees from treated cotton

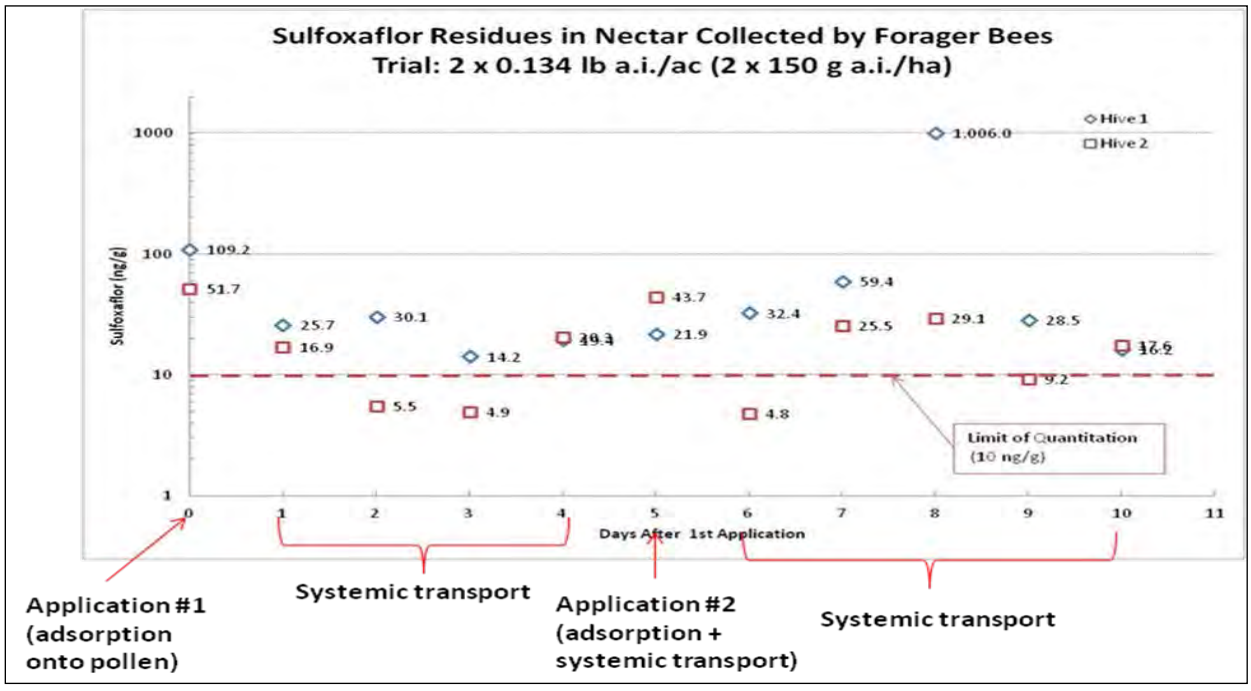

Figure D-2. Sulfoxaflor residues reported in nectar collected by forager bees from treated cotton

Biological measurements of hive attributes indicated that foragers were able to obtain sufficient nectar to maintain the number of foragers in hives following 10 days exposure in tunnels treated with sulfoxaflor. However, pollen reserves were exhausted in all treatments by 10DAE, indicating the quantity and/or quality of cotton pollen was insufficient to maintain pollen stores.

This apparent lack of pollen due to the artificial confinement likely influenced the reduction in brood condition on 10DAE and 17DAE relative to 3DBE. The lack of a concurrent control precluded evaluation of sulfoxaflor effects separate from those likely caused by the tunnel enclosure itself.

***Phacelia* Residue Study (MRID 48446601).** A semi-field study was conducted to investigate the residues of sulfoxaflor (GF-2626) in nectar, pollen and whole plant tissue after four types of applications. Specifically, the test substance was applied at rates of 24 g a.i./ha (treatment groups Tl and T3) and 48 g a.i./ha (treatment groups T2 and T4) in separated tunnels. A fifth group (tunnel) left untreated served as control. Applications in treatment group T I and T2 were conducted before flowering, applications in treatment group T3 and T4 were made during flowering and during daily bee flight. All applications were made with a rate of 400 L water/ha. Commercial bee colonies were placed in tunnels (approx. 200 rn^2) on plots with *Phacelia tanacetifolia.* Condition of the colonies and the development of the bee brood were assessed once before the start of exposure of the honeybees in the tunnels.

In order to evaluate the magnitude of residues of the test item GF-2626, nectar stomachs from forager bees, pollen samples from pollen traps, and the treated phacelia plants were taken for analysis on days 0, 5, and 6 after application in T3 and T4 treatments (10, 15 and 16 days after application in T1 and T2 treatments; **Table D-2**).

Table D-2. Residues of sulfoxaflor detected in nectar collected from foragers, pollen collected from hive traps, and whole *Phacelia* (MRID MRID 48446601)

Day	Treatment	Application Rate (g ai/ha)	Nectar (mg/kg)	Pollen (mg/kg)	Whole Plant (mg/kg)
0DAA	T1	24 (before flower)	n.d.	n.d.	n.d.
	T2	48 (before flower)	n.d.	n.d.	0.034
	T3	24 (during flower)	0.04-0.05	0.29	0.52
	T4	48 (during flower)	0.05-0.09	0.81	1.48
5DAA	T1	24 (before flower)	n.d.	n.d.	n.d.
	T2	48 (before flower)	n.d.	n.d.	n.d.
	T3	24 (during flower)	n.d.	n.d.	0.027
	T4	48 (during flower)	0.01	0.019	0.052
6DAA	T1	24 (before flower)	n.d.	n.d.	n.d.
	T2	48 (before flower)	n.d.	n.d.	n.d.
	T3	24 (during flower)	n.d.	0.016	0.048
	T4	48 (during flower)	n.d.	0.033	0.051

For treatments T3 and T4 (applied during flowering), residues in nectar measured on 0DAA ranged from 0.04 to 0.09 mg a.i./kg respectively, while those in pollen were up to 10X greater (0.29 & 0.81 in T3 and T4, respectively). Sulfoxaflor residues declined sharply from 0DAA to 5DAA in treatments T3 and T4, with levels below the detection limit of 0.01 mg/kg in T3 and 0.019 mg/kg in T4. On 6DAA, residues were slightly higher in T4 (0.033 mg/kg) and were just above detection in T3 (0.016 mg/kg).

The highest residues of sulfoxaflor were observed in whole plant on 0DAA, ranging from 0.034, 0.52 and 1.48 mg a.i./kg in T2, T3 and T4 respectively. On 5DAA and 6DAA, sulfoxaflor residues were only detected in the T3 and T4 treatments at 0.03 to 0.05 ppm. Residues of the primary metabolite (474) were below analytical detection except in whole plant on 6DAA (T4).

Overall, a dose-dependent increase in residues occurred on 0DAA in nectar, pollen and whole plant tissues. This was followed by a substantial decrease to about 3% – 10% of 0DAA residues by 5DAA across all matrices.

***Phacelia* Residue Study (MRID 48445806).** This semi-field tunnel study was conducted to determine the effects of sulfoxaflor TEP GF-2032 on the honeybee, *Apis mellifera carnica* L. This study included seven treatment groups of the test item GF2032 applied at calculated rates of 99, 50, 24, 13.6 and 6.5 g a.i./ha in separated tunnels. All applications were conducted when bees were actively foraging (> 5 bees/m^2) during daily bee-flight and with a spay volume of 300 L water/ha. The effect of the test item was examined on small bee colonies in tunnels (approx. 100 m^2) placed on plots with *P. tanacetifolia.*

Residues in pollen collected from sulfoxaflor treated plots on 7DAA showed somewhat of a dose-dependent increase with sulfoxaflor application rate although residues in T2/50.0 g ai/ha (0.225 ppm) were lower than one might expect compared to T1/99.2 g ai/ha (1.013 ppm) or T3/24 g ai/ha (0.612 ppm; **Table D-3**). Residues of the primary metabolite (X474) were low (approaching or below the limit of detection of 0.01 ppm).

Table D-3. Results from pollen residue analysis of sulfoxaflor treated *Phacelia* plots measured 7DAA (MRID 48445806)

Fraction	Sample No.	Treatment	Residue XDE-208 mg/kg	Residue X11719474 mg/kg
Pollen	CSR 4228-001	C	ND	ND
Pollen	CSR 4228-002	T1	1.013	<0.01
Pollen	CSR 4228-003	T2	0.225	<0.01
Pollen	CSR 4228-004	T3	0.612	0.012
Pollen	CSR 4228-005	T4	0.043	ND
Pollen	CSR 4228-006	T5	0.064	0.023

Values between 0.003 (30% of the LOQ) and 0.01 (LOQ) mg/kg are reported as <0.01 mg/kg
ND = Not detected (residue value was less than 30% of the LOQ)

T1 = 99; T2 = 50, T3 = 24, T4=13.6 and T5= 6.5 g a.i./ha applications

Samples were collected from the T3/24 g ai/ha and control plots on 0DBA for residue analysis in flowers (**Table D-4**). Samples were also collected on 0DAA, 3DAA, 5DAA and 7DAA from the T3/24 g ai/ha treated plot. Residues of sulfoxaflor and X474 metabolite were both below detection levels (<0.01 ppm) prior to application. Just after application (0DAA), 1.8 ppm of sulfoxaflor was detected in flowers, which declined by about 10X by 3DAA and about 2X further by 5DAA and 7DAA. By 7DAA, sulfoxaflor residues in flower from the T3/24 g ai/ha (0.096 ppm) were about 6X lower than corresponding residues in pollen sampled at the same time and treatment (0.612 ppm). The metabolite X11719474 was below the limits of analytical detection throughout the exposure period.

Table D-4. Results from flower residue analysis of *Phacelia* plots treated with 24 g ai/ha sulfoxaflor (MRID 48445806)

Fraction	Sample No.	Timing / Treatment	Residue XDE-208 mg/kg	Residue X11719474 mg/kg
Flowers	CSR 4228-007	0 DBA / C	ND	ND
Flowers	CSR 4228-008*	0 DBA / T3	ND	ND
Flowers	CSR 4228-010	0 DAA / T3	1.755	<0.01
Flowers	CSR 4228-012	3 DAA / T3	0.193	<0.01
Flowers	CSR 4228-014	5 DAA / T3	0.065	<0.01
Flowers	CSR 4228-016	7 DAA / T3	0.096	<0.01

Values between 0.003 (30% of the LOQ) and 0.01 (LOQ) mg/kg are reported as <0.01 mg/kg
ND = Not detected (residue value was less than 30% of the LOQ)
DBA = Days before application

Pumpkin Residue Study (MRID 48755601). This non-good laboratory practice (GLP) study was conducted to measure residues of sulfoxaflor in various plant tissues of a pumpkin crop following foliar application of low and high rates of sulfoxaflor. Application rates were 25 and 100 g a.i./ha (0.0223 and 0.0892 lbs/A). Each treatment (replicated 4 times) included one treated plot in which sulfoxaflor, formulated as a 24% solution, was applied to pumpkins as a foliar spray at a target rate of 25 g a.i./ha (low rate) and 100 g a.i./ha (high rate). Sulfoxaflor was applied starting at 7 am on 25-July-2001 (Week 6) and 8-August-2011 (Week 8) using a backpack sprayer in spray volumes of 197 L/ha.

Staminate flowers first appeared 4 weeks after planting, and tissue sampling was conducted during weeks 6, 7, and 8 post-planting when plants reached peak flowering. Five types of plant tissues were collected for residue analysis: nectar, pollen, nectary, peduncle (stem), and leaf tissue. Samples were analyzed for residues of sulfoxaflor using a liquid chromatography mass spectrometers (LC/MS/MS). Sulfoxaflor was applied on the Monday of weeks 6 and 8 post-planting. On Tuesday and Thursday of each week, wax-coated paper bags were placed over staminate flower buds that had not yet bloomed to prevent pollinator visits. Bags with open flowers were removed the following day and brought to the laboratory to extract nectar and pollen. Therefore, residue samples reflect systemically translocated chemical from a minimum of 2 to 4 days after pesticide application.

Residues in nectar averaged over the three sampling weeks were 2.3, and 9.5 ng/g for the low and high rates of sulfoxaflor, respectively (**Table D-5**). Residues in pollen averaged over sampling weeks were 11.2, and 76.8 ng/g for the low and high rates of sulfoxaflor, respectively. Sulfoxaflor residues were not detectable in pollen after the first foliar application of the low rate but averaged 33.5 ng/g after the second application. For the low and high rates of sulfoxaflor, residues averaged 41.1 and 310.7 ng/g in leaf tissue.

Table D-5. Mean, minimum and maximum residue levels of sulfoxaflor in pumpkin pollen, nectar and leaf tissue (MRID 48755601)

Rate - foliar application of sulfoxaflor	Weekly sampling period after planting			
	Week 6 (foliar application of sulfoxaflor)	Week 7 (no treatment)	Week 8 (foliar application of sulfoxaflor)	

(g a.i./ha)	Residues of sulfoxaflor in pollen (ng/g) [a]									
	Mean	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**	**Average [b]**
25	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	33.5	<LOQ	84.3	11.2
100	29.7	<LOQ	53.8	<LOQ	<LOQ	<LOQ	200.7	53.7	380.0	76.8
	Residues of sulfoxaflor in nectar (ng/g) [a]									
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Average [b]
25	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	7.0	<LOQ	28.0	2.3
100	26.1	<LOQ	26.1	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	9.5
	Residues of sulfoxaflor in leaf tissue (ng/g) [a]									
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Average [b]
25	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	123.2	87.2	198.0	41.1
100	124.4	70.6	263.0	<LOQ	<LOQ	<LOQ	807.8	261.0	1270.0	310.7

[a] Residues reported from pooled samples collected on Wed. and Fri.; sulfoxaflor was applied on Mon.

[b] Averaged over the three sampling weeks, reported in ng/g.

LOQ reported to be 25 ng/g (ppb)

Proposed Registration of the New Active Ingredient Sulfoxaflor for Use on Multiple Commodities, Turfgrass and Ornamentals

Approved by: Lois Rossi

Lois Rossi, Director
Registration Division

Date: January 14, 2013

PER 000170

Proposed Registration of the New Active Ingredient Sulfoxaflor

Regulatory Rationale

The Agency is proposing to conditionally grant the registration of the new active ingredient sulfoxaflor, formulated as a technical product and two end use products. The proposed new uses include barley, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables, low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, root and tuber vegetables, small fruit vine climbing (except fuzzy kiwifruit), soybean, stone fruit, succulent, edible podded and dry beans, tree nuts, triticale, turfgrass (commercial sodfarms and grass grown for seed), watercress, and wheat. Methods of application include aerial and ground broadcast, in addition to chemigation for potato. The maximum single application rate initially proposed by the registrant was 0.133 lbs ai/acre; the Agency is proposing a maximum single application rate of 0.09 lbs ai/acre to reduce potential risk to pollinators.

I. Chemical Information

Chemical Name: sulfoxaflor; cyanamide, N-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl] λ^4-sulfanylidene]

EPA PC Code: 005210

Chemical Abstracts Service (CAS) Number: 946578-00-3

IRAC MoA Classification: Group 4C: Nicotinic acetylcholine receptor agonists, sulfoxamines

Mode of Action: Sulfoxaflor is an insecticide that acts through a unique interaction with the nicotinic acetylcholine receptor in insects. While sulfoxaflor acts on the same receptor as the neonicotinoids, it is classified as its own subgroup. It is an agonist of the nicotinic acetylcholine receptor (nAChR) and exhibits excitatory responses including tremors, followed by paralysis and mortality in target insects. The structure of sulfoxaflor makes it stable in the presence of a monooxygenase enzyme that was shown to degrade a variety of neonicotinoids in IRAC Group 4A, resulting in a lack of cross-resistance demonstrated in laboratory experiments.

Registrant: DOW AgroSciences LLC

Proposed Products: Sulfoxaflor is proposed for registration as EPA Reg. 62719-AGR/62719-631 (Sulfoxaflor Technical), 62719-AEL/62719-625 (Transform WG), and EPA Reg. 62719-AEG/62719-623 (Closer SC).

II. Human Health Risk

A summary of the human health effects and risk of sulfoxaflor as assessed in the Agency document entitled "*Sulfoxaflor—New Active Ingredient Human Health Risk Assessment of Uses on Numerous Crops*" is provided below.

A. Summary of Toxicological Effects

Sulfoxaflor is the only member of a new class of insecticides and is a highly efficacious activator of the nicotinic acetylcholine receptor (nAChR) in insects. Toxicity and mechanistic studies in rats, rabbits, dogs and mice indicate that sulfoxaflor is an activator of the mammalian nAChR as well, but to a much lesser degree and in a species-specific manner. The database of guideline toxicity studies indicates that the nervous system and liver are the target organ systems, resulting in developmental toxicity, hepatotoxicity, and other apical effects.

Developmental/offspring toxicity, manifested as skeletal abnormalities and neonatal deaths, was observed in rats only. The skeletal abnormalities, including forelimb flexure, bent clavicles, and hindlimb rotation, likely resulted from skeletal muscle contraction due to activation of the skeletal muscle nAChR *in utero*. Contraction of the diaphragm, also related to skeletal muscle nAChR activation, prevented normal breathing in neonates and resulted in increased mortality in the reproduction studies. Furthermore, targeted studies indicate that offspring effects are dependent upon *in utero* exposure to sulfoxaflor. The skeletal abnormalities were observed at high doses in the developmental and reproduction studies while decreased neonatal survival was observed at slightly lower levels (e.g., mid- and high-dose animals).

Exposure to sulfoxaflor and its major metabolites resulted in hepatotoxicity in several guideline studies. For example, sulfoxaflor caused liver weight and enzyme changes, hypertrophy, proliferation, and tumors in subchronic and chronic studies. Short-term studies with metabolites resulted in similar liver effects. For sulfoxaflor, hepatoxicity occurred at lower doses in long-term studies compared to short-term studies.

In addition to the developmental and hepatic effects, treatment with sulfoxaflor resulted in decreased food consumption and body weight as well as changes in the male reproductive system. Decreased body weight, body weight changes, and food consumption were observed during the first few days of several oral studies at the mid- and high-dose levels. As a result of decreased feeding early in the studies, body weights were typically lower in the mid- and high-dose groups compared to the controls, although the differences were not generally statistically significant. Decreased palatability is a likely contributor to this effect as body weight decreases were often observed at study initiation but were comparable to control animals within several weeks.

Effects in the male reproductive organs were observed in the chronic/carcinogenicity study in rats that included increased testicular and epididymal weights, atrophy of seminiferous tubules, and decreased secretory material in the coagulating glands, prostate, and seminal vesicles. Additionally, there was an increased incidence of interstitial cell (Leydig cell) tumors. The Leydig cell tumors observed after exposure to sulfoxaflor are not considered treatment related due to the lack of dose response, the lack of statistical significance for the combined tumors (unilateral and bilateral), and the high background rates for this tumor type in F344 rats. The primary effects on male reproductive organs are considered secondary to the loss of normal testicular function due to the size of the interstitial cell (Leydig Cell) adenomas. Consequently, the secondary effects to the male reproductive organs are also not considered treatment related.

Clinical indications of neurotoxicity were only observed at high doses in the acute neurotoxicity study in rats. At the highest dose tested, muscle tremors and twitches, convulsions, hindlimb splaying, increased lacrimation and salivation, decreased pupil size and response to touch, gait abnormalities and decreased rectal temperature were observed. Decreased motor activity was also observed in the mid- and high-dose groups. Since the neurotoxicity was observed only at a very high dose and many of the effects are not consistent with the perturbation of the nicotinic receptor system (e.g., salivation, lacrimation, and pupil response), it is unlikely that these effects are due to activation of the nAChR.

Finally, tumors were observed in chronic rat and mouse studies. In rats, significant increases in the incidence of hepatocellular adenomas and combined adenomas and/or carcinomas in the high-dose males were observed when compared to controls. In mice, there were significant increases in hepatocellular adenomas, carcinomas, and combined adenomas and/or carcinomas in high dose males when compared to controls. In female mice, there was an increase in the incidences of carcinomas at the high dose. Although this increase did not reach statistical significance, the incidences exceeded the historical control range for this tumor type and were corroborated with the presence of non-neoplastic lesions at this dose. EPA determined that the liver tumors in mice were treatment-related. Using data from several mechanistic studies, EPA also determined that the liver effects in mice are non-linear (threshold) in their mode of action (MoA) and the MoA for the liver tumors is consistent with a constitutive androstane receptor (CAR) mediated, mitogenic mode-of-action. Leydig cell tumors were also observed in the high-dose group of male rates, but it was determined that the tumors were not related to treatment. There was also a significant increase in the incidence of preputial gland tumors in male rats in the high-dose group. Marginal increases were also observed in the low- and mid-dose groups; however, the incident values for these groups were within the range of historical control values. Preputial gland tumors are not commonly diagnosed in bioassay studies. The available data were inadequate to draw confident conclusions regarding this response due to the small sample size and lack of histopathology data on all animals. Thus, it was not possible to determine whether the preputial gland tumors are due to treatment. If the response is positive, this would be an unusual finding. Because the tumors could not be discounted, they were used in the suggestive classification.

Based on the weight of evidence, including mode-of-action data, the EPA determined that there is "Suggestive Evidence of Carcinogenic Potential" for sulfoxaflor, based on the preputial gland tumor response seen in rats. Suggestive evidence of carcinogenicity means there is some limited potential for carcinogenic effects but the evidence is judged not sufficient for linear quantification of cancer risk in humans as the nature of the data generally does not support one. The data here do not support a linear quantification of the cancer risk because the treatment-related liver tumors in mice are produced by a mode-of-action subject to a threshold. In addition, the Leydig cell tumors were not treatment-related, and the preputial gland tumors only occurred at the high dose in one sex of one species; therefore, EPA concluded that the evidence of potential carcinogenicity was weak and that that quantification of risk using a non-linear approach (i.e., reference dose (RfD) will adequately account for all chronic toxicity, including any potential carcinogenic effects, that could result from exposure to sulfoxaflor. The current NOAEL of 5.13 mg/kg/day used for chronic dietary risk assessment is significantly (4x) lower than the dose where tumors were observed $\geq$ 21.3 mg/kg/day.

In addition, EPA determined there was sufficient evidence to support a developmental mode-of-action (i.e., activation of the nAChR) accounting for the skeletal abnormalities and increased mortality observed in the rat. Furthermore, there was sufficient evidence to support that rats are uniquely sensitive to these developmental effects, informing interspecies uncertainty. Although the database indicates that the developmental effects are unlikely to be relevant to humans, the effects will be considered as relevant to humans unless additional information to the contrary is provided. Data are sufficient to support reducing the interspecies uncertainty factor to 3X for the developmental effects.

B. FQPA Safety Factor

EPA has determined that reliable data show the safety of infants and children would be adequately protected if the FQPA SF for sulfoxaflor were reduced to 1x. That decision is based on the following findings:

1. The toxicity database for sulfoxaflor is complete.

2. The level of concern for neurotoxicity is low because the effects are well characterized, the dose-response curve for these effects is well characterized, and clear NOAELs have been identified.

3. Although there is evidence of quantitative susceptibility in the DNT study, based on decreased survival of offspring up to postnatal day 4, the endpoints and doses selected for risk assessment are protective for these effects; further, EPA's degree of concern for human susceptibility is reduced based on the special studies submitted in support of the mode of action.

4. There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessments were performed based on 100% CT and either maximum or average residue levels from field trials. EPA made conservative (protective) assumptions in the ground and surface water modeling used to assess exposure to sulfoxaflor in drinking water. Although some refinements were used in the exposure assessment, the dietary and drinking water assessments will still result in the upper-bound estimates of exposure.

C. Toxicological End Points and Doses Used in the Human Health Risk Assessment

1. Acute: EPA established an acute reference dose (aRfD) and an Acute Population Adjusted Dose (aPAD) for sulfoxaflor for the general population, which included groundwater exposure to the metabolites of sulfoxaflor, of 0.25 mg/kg body wt/day, based on the "No Observable Effects Level" (NOAEL) of 25 mg/kg body weight/day from the acute neurotoxicity study in rats and an uncertainty factor of 100. In this study, decreased motor activity was observed at the "lowest observed adverse effect level" (LOAEL) of 75 mg/kg body wt/day. EPA also established an aRfD and an aPAD for sulfoxaflor for females 13-50 years of age, which included surface water exposure to the sulfoxaflor parent compound, of 0.06 mg/kg body wt/day, based on the "No

Observable Effects Level" (NOAEL) of 1.8 mg/kg body weight/day from the developmental neurotoxicity study in rats and an uncertainty factor of 30. In this study, decreased neonatal survival (PND 0-4) was observed at the "lowest observed adverse effect level" (LOAEL) of 7.1 mg/kg body wt/day.

2. Chronic Dietary: EPA established a chronic reference dose (cRfD) and a Chronic Population Adjusted Dose (cPAD) for sulfoxaflor of 0.05 mg/kg body wt/day, based on the NOAEL of 5.13 mg/kg body wt/day from the chronic/carcinogenticty study in rats and an uncertainty factor of 100. In this study, liver effects including increase blood cholesterol, liver weight, hypertrophy, fatty change, single cell necrosis and macrophages were observed at the LOAEL of 21.3 mg/kg body wt/day.

3. Short- and Intermediate-Term Dermal and Inhalation: The same endpoint (toxic effect) and dose (NOAEL) were selected for assessing short- and intermediate-term dermal and inhalation exposure. EPA selected the NOAEL of 1.8 mg/kg body wt/day from the developmental neurotoxicity study based on decreased neonatal survival (PND 0-4) observed at the LOAEL of 7.1 mg/kg body wt/day. A dermal absorption factor of 2.4% and an inhalation absorption factor of 100% were used in the relevant exposure assessments.

The current risk metric for assessing short- and intermediate-term occupational exposure to sulfoxaflor is a margin of exposure (MOE) that is less than 30. At a baseline level of personal protective equipment (PPE), estimated occupational MOEs range from 80 to 4,700,000, and the vast majority of the estimates are greater than 300. All estimated occupational MOEs indicate that risks are below EPA's level of concern.

4. Cancer: EPA has classified sulfoxaflor as "Suggestive Evidence of Carcinogenic Potential" based on the preputial gland tumor response observed in rats. The Agency has determined that quantification of risk using a non-linear approach (i.e., reference dose (RfD)) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to sulfoxaflor.

D. Cumulative Effects

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not found sulfoxaflor to share a common mechanism of toxicity with any other substances, and sulfoxaflor does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has assumed that sulfoxaflor does not have a common mechanism of toxicity with other substances.

E. Aggregate Risk Assessment

1. Dietary (Food + Drinking Water) Risk:

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™ (v. 2.03), uses food consumption data from the U.S. Department of Agriculture's (USDA's) Continuing

Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. EPA has assumed 100% of crops covered by the registration request are treated with sulfoxaflor.

Acute Dietary Risk: The data used in the acute assessment reflect several refinements relative to a screening-level assessment. Maximum residue values from field trials were used rather than tolerance-level residue estimates. The field trials are designed to produce high-end residue levels in crops and although these values are less than the tolerance value, their use in risk assessment is considered to be very health protective. For crop groups, the residue values were translated from representative crops to the other crops in the group. For processed commodities, empirical processing factors were used for all commodities unless an empirical factor was not available, in which case the DEEM default estimate was used. Residue estimates for livestock were derived using maximum observed residues in the cattle and hen feeding studies.

Acute dietary risk estimates range from 4% to 16% of the acute population-adjusted dose (aPAD), with the highest risk estimates being for children 1-2 years old and females 13-49 years old. Generally, EPA is concerned when exposure estimates exceed 100% of the population-adjusted dose (PAD). Even with the conservatisms in the assessment, acute dietary risk estimates are below EPA's level of concern.

Chronic Dietary Risk: For the chronic assessment, the same refinements were made as those described for the acute assessment, with two exceptions: (1) average residue levels from crop field trials were used rather than maximum values and (2) average residues from feeding studies, rather than maximum values, were used to derive residue estimates for livestock commodities. The use of average residue values in chronic risk assessment is appropriate since residue levels in foods would be averaged over the long-term consumption patterns reflective of chronic assessments. As with the acute assessment, the residues from crop field trials are considered to be high-end values with built-in conservatism, even when average residue values are used.

Chronic dietary risk estimates range from 5% to 18% of the chronic population-adjusted dose (cPAD) with the highest risk estimate estimated for infants. All of the risk estimates are below EPA's level of concern.

2. Residential Risk:

Residential exposures and risk were not assessed because the proposed uses of sulfoxaflor do not involve applications by homeowners or commercial applicators in residential settings at this time.

3. Aggregate Risk:

There are no residential uses for sulfoxaflor; therefore the aggregate exposure and risk assessments include acute and chronic dietary (food and water) only and are reported above. There are no aggregate risk concerns for the proposed new uses of sulfoxaflor.

F. Occupational Risk Assessment

1. **Handler Exposure and Risk:**

Dermal and inhalation occupational handler scenarios for the proposed uses resulted in estimated MOEs that are greater than 30 and therefore are not of concern. This was determined at the baseline level of PPE (i.e., baseline clothing, no gloves, and no respirator) and engineering controls (enclosed cockpit) for aerial applications.

2. **Occupational Postapplication Exposure and Risk:**

Occupational workers who enter treated fields to perform post-application activities such as hand weeding and scouting may be exposed dermally to sulfoxaflor residues. Based on the use pattern, workers may be exposed to short- and intermediate-term exposure durations. Post-application dermal exposure and risk estimates resulted in MOEs greater than 30 and are not of concern.

A quantitative post-application inhalation exposure assessment was not performed for sulfoxaflor at this time primarily because it has a low vapor pressure and it is applied at low application rates. Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational handlers. This assessment resulted in risk estimates that did not exceed EPA's level of concern at baseline inhalation PPE. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios. Furthermore, the Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

III. Environmental Risk

A summary of the environmental fate and ecological effects and risks of sulfoxaflor as assessed in the Agency document entitled *"Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration"* is provided below.

A. Environmental Fate

Sulfoxaflor has a low potential for volatilization from dry and wet surfaces (vapor pressure= 1.9×10^{-8} torr and Henry's Law constant= 1.2×10^{-11} atm m^3 $mole^{-1}$, respectively at 25 °C). The chemical is characterized by a water solubility ranging from 550 to 1,380 ppm. Partitioning coefficient of sulfoxaflor from octanol to water (K_{ow}= 6; Log K_{ow}= 0.802) suggests low potential for bioaccumulation in aquatic organisms such as fish.

Sulfoxaflor reaching the soil system is subjected to rapid aerobic bio-degradation ($t_{½}$ <1 day) while that reaching foliage may enter the plant tissue and persist much longer. Sulfoxaflor has shown to be stable to hydrolysis/photolysis on soil and in aquatic environments. In field studies,

sulfoxaflor has shown similar vulnerability to aerobic bio-degradation in nine out of ten terrestrial field dissipation studies on bare-ground/cropped plots (half-lives were <2 days in nine cropped/bare soils in CA, FL, ND, ON and TX and was 8 days in one bare ground soil in TX).

The chemical is characterized by very high to high mobility (K_{foc} ranged from 11-72 mL g^{-1}). Rapid soil degradation is expected to limit chemical amounts that may potentially leach and contaminate ground water. Contamination of groundwater by sulfoxaflor will only be expected when excessive rain occurs within a few days of multiple applications in vulnerable sandy soils. Contamination of surface water by sulfoxaflor is expected to be mainly related to drift and very little due to run-off. This is because drifted sulfoxaflor that reaches aquatic systems is expected to persist while that reaching the soil system is expected to degrade quickly with slight chance for it to run-off.

In contrast to sulfoxaflor parent, the major degradate X-474 and two other degradates (X-540 and X-457) are expected to be highly persistent in aerobic soil/aquatic systems. Adsorption data for these degradates indicate that they can be characterized by very high to high mobility for X-474 (K_{foc} ranged from 7-68 mL g^{-1}) and very high mobility for X-457 and X-540 (K_{foc} ranged from 2-44 mL g^{-1} for X-457 and K_{foc} ranged from 1-25 mL g^{-1} for X-540). Both surface and ground water contamination is expected from these three degradates following leaching drift/run-off events. The major degradate X-474 is expected to dominate the exposure resulting from use of sulfoxaflor.

B. Ecological Risk

Ecological risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of integrating the results of exposure and ecotoxicity data is called the quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic (RQ = Exposure/Toxicity). RQs are then compared to EPA's levels of concern (LOCs). The LOCs are criteria used by the Agency to indicate potential risk to non-target organisms. The criteria indicate whether a pesticide, when used as directed, has the potential to cause adverse effects to non-target organisms.

1. Aquatic Organisms

Fish: Sulfoxaflor is classified as practically non-toxic to freshwater and saltwater fish on an acute exposure basis. As a result, maximum acute and chronic RQ values for freshwater and saltwater fish determined with the crop exposure scenario producing the highest aquatic estimate exposure concentrations (EECs), NC Cotton, are one to three orders of magnitude below the listed and non-listed species LOC values of 0.5 and 0.05, respectively.

Invertebrates: Maximum acute RQ values for freshwater invertebrates are three orders of magnitude below the acute risk to listed species LOC while that for saltwater invertebrates marginally exceeds (RQ=0.08) the acute risk to listed species LOC of 0.05. Maximum chronic RQ values do not exceed the chronic risk LOC (1.0) for either freshwater or saltwater invertebrates.

Since the maximum acute RQ for saltwater invertebrates exceeds the acute risk to listed species LOC based on total residues of interest, acute RQ values were re-calculated with refined EECs that include only the toxicological residues of concern (parent + X-540) for those exposure scenarios with RQs that exceed the LOC. These refined RQ values are well below LOCs for non-listed and listed species.

For estimating acute risks to benthic invertebrates, risk quotients were determined using peak pore water EECs divided by the lowest acute toxicity endpoint for fresh and saltwater water column invertebrates, since acute toxicity data were not available from sediment toxicity studies. For estimating chronic risks to benthic invertebrates, risk quotients were determined by dividing the highest 21-d average EEC in pore water by the lowest pore water NOAEC obtained for the midge (freshwater) and water column exposure NOAEC for mysid shrimp. For fresh water benthic invertebrates, a slight exceedance (RQ=0.08) of the acute risk to listed species LOC and the chronic risk (RQ=1.4) LOC is indicated.

Since the maximum acute RQ for saltwater benthic invertebrates using the total residues of interest exceeds the acute risk to listed species LOC and the maximum chronic RQ for freshwater benthic invertebrates the chronic risk LOC, acute and chronic RQ values for those scenarios exceeding the LOCs were re-calculated using just the residues of toxicological concern (parent and X-540). These refined RQ values are well below acute and chronic risk LOCs for non-listed and listed species.

Plants: None of the risk quotients calculated for vascular and non-vascular aquatic plants using the crop exposure scenario with the highest acute and chronic EECs in surface water (NC cotton) exceed the LOC for listed or non-listed aquatic plant species.

2. Terrestrial Organisms

Mammals: Maximum acute mammalian RQ values are all below 0.1 which indicates a low acute risk potential to listed and non-listed mammals consuming the modeled forage items.

Potential chronic risks to mammals are derived using a dietary-based NOAEL of 100 ppm from a 2-generation reproduction study with the rat and EECs for the crop exposure scenario yielding the maximum residues on forage items (2 x 0.133 lb ai/A). The chronic dietary-based RQ values range from 0.03 (fruits, pods, seeds, large insects) to 0.5 (short grass). Since these chronic RQ values are all below the chronic risk LOC of 1.0, the potential for chronic risks to mammals based on a dietary approach is considered low.

Potential chronic risks to mammals are also evaluated using a dose-based approach which relies on a NOAEL of 6.07 mg a.i./kg bw/d from the same 2-generation toxicity rat study. This dose-based NOAEL is adjusted to account for different size classes of mammals. These adjusted values are used to interpret the dose-based EECs calculated for the same mammalian size classes. The overall range in chronic RQ values is from 0.01 to 3.8, and the potential for chronic risks to mammals is identified for all crop scenarios for at least one dietary category.

Birds: For sulfoxaflor, avian dose-based acute RQs are based on the zebra finch acute oral toxicity data (LD_{50} > 80 mg a.i./kg bw) which reflects the concentration above which dose-dependent effects of regurgitation were observed. Thus, a value of 80 mg a.i./kg bw is used as a conservative screen for acute risks to birds. Acute dose-based RQ values are based on LD_{50} values adjusted differences in body weight for birds (20, 100, 1000g) (adjusted LD_{50} =86.4, 110 and 155 mg a.i./kg bw, respectively) and modeled acute dose-based EECs for various use scenarios and diet categories, and a sulfoxaflor-specific foliar DT_{50} of 12.3 days. The overall range in avian acute RQ values is from <0.01 to 0.70, and the potential for chronic risks to birds (including reptiles and terrestrial-phase amphibians) is identified for all crop scenarios for at least one dietary category. No avian subacute acute risk is identified with the dietary-based approach, as RQ values are all well below the acute risk to listed species LOC of 0.1. Chronic dietary-based RQs range from 0.02 to 0.27, thus indicating a low potential for chronic risks to birds.

Plants: The NOAEC values from seedling emergence and vegetative vigor toxicity tests of terrestrial plants are above the maximum single application rate of 0.133 lb ai/A. Therefore, a low potential for risk to listed and non-listed terrestrial plants is expected based on the proposed use profile for sulfoxaflor.

Bees: Sulfoxaflor is classified as very highly toxic with acute oral and contact LD_{50} values of 0.05 and 0.13 µg a.i./bee, respectively, for adult honey bees (*Apis mellifera*). For larvae, a 7-d oral LD_{50} of >0.2 µg a.i./bee was determined (45% mortality occurred at the highest treatment of 0.2 µg a.i./bee). Sulfoxaflor's primary metabolite (X-474) is practically non-toxic to the honey bee. The acute oral toxicity of sulfoxaflor to adult bumble bees (*Bombus terrestris*) is similar to the honey bee, whereas its acute contact toxicity is about 20X less toxic for the bumble bee. Sulfoxaflor did not demonstrate substantial residual toxicity to honey bees exposed via treated and aged alfalfa (*i.e.*, mortality was ≤15% at maximum application rates).

For the initial Tier 1 screen, the dietary and contact exposure routes are considered. For generating RQs, dietary-based exposure values are compared to oral toxicity data for larvae and adult worker bees while contact exposure values are compared to acute contact toxicity data for adult worker bees. The initial screening-level RQs exceeded the proposed LOC of 0.4 for adults (oral and contact) exposures. Additional refinements of the Tier 1 exposure estimates were conducted using chemical-specific data on residues in pollen and nectar. By combining the maximum reported residues of sulfoxaflor in pollen and nectar with the estimated consumption rates, a total oral dose is estimated. This oral dose is then divided by the applicable acute oral LD_{50} (0.0515 µg ai/bee for adult workers and >0.2 µg ai/bee for larvae, respectively) to derive the acute RQ values. This refinement resulted in RQs ranging from <0.8 to 5.7 which exceed the LOC for acute risk (0.4). This indicates that risk to honey bee colonies cannot be precluded and analysis of effects at the whole hive level is warranted (Tier 2).

It is important to note that the Tier 1 refinement is based on the maximum reported residues of sulfoxaflor in pollen and nectar. Based on the estimated median consumption rates of pollen and nectar, it is clear that the oral exposure of adult and larval honey bees is dominated by the consumption of nectar, with more than 90% of the total consumed food source represented by nectar. Given the importance of nectar as a source of food and potential contaminant exposure, the concentration in nectar that would meet or exceed the proposed acute risk LOC of 0.4 was

determined. Based on the acute LD_{50} of 0.0515 µg a.i./bee and a consumption rate of 292 mg/d for adult nectar foragers, a concentration of > 0.07 ppm in nectar would result in an acute oral RQ that meets or exceeds the proposed LOC of 0.4. The adult nectar forager caste was chosen because it has the highest estimated nectar consumption rate among the various castes assessed. A comparison of each of the 88 reported residues of sulfoxaflor in cotton nectar reveals that only 4 values (5%) exceeded the 0.07 ppm LOC-based threshold. Three of these values are within a factor of two, but one value (1.0 ppm, day 8, 2 x 0.134 lb a.i./A, hive 1) is about 14X above the residue equivalent to the LOC. The vast majority of sulfoxaflor residues in nectar (88%) are less than half the 0.07 ppm LOC-based threshold in nectar. The Agency is proposing to reduce the maximum single application rate to 0.09 lbs ai/acre. At this application rate, the concentration in nectar is at or below 0.07 ppm, which does not exceed the LOC of 0.4. While the concentration of sulfoxaflor in pollen would add to the total dose estimated for nectar foragers, bees, the contribution is very minor and does not affect this interpretation of the results.

A detailed analysis of six available Tier 2 semi-field (tunnel) studies was conducted in order to confirm or refute the risks identified from the Tier 1 assessment on honey bees. Five of the six semi-field studies used application rates ranging from 3 to 67% of the single maximum application rate of 0.133 lb a.i./A initially proposed for the US. The one semi-field study that used maximum US application rates was intended for quantifying residues in plant matrices, and thus, has limited biological effects information.

Direct Effects on Bees: Direct effects on bees are those that result directly from interception of spray droplets or dermal contact with and ingestion of foliar residues. Results from the Tier 2 semi-field studies suggest that at the application rates used (3-67% of US maximum), the direct effects of sulfoxaflor on adult forager bee mortality, flight activity and the occurrence of behavioral abnormalities is relatively short-lived, lasting 3 days or less. The direct effect of sulfoxaflor on these measures at the initially proposed maximum application rate in the US is presently not known.

Brood Development: In the two submitted studies most appropriate to determine brood effects, there was a large increase in brood termination rate observed for the reference toxicant (fenoxycarb, applied at ~2X the maximum labeled rate) compared to the control for these two studies, which indicates that despite the high larval mortality in control hives, a major catastrophic impact on brood could be detected. Although uncertain due to high mortality of larvae in controls, the effects of sulfoxaflor applications on brood development were similar to that of the controls. These results suggest that the study design allows for the detection of catastrophic losses to the brood, as seen in the hives exposed to fenoxycarb, and that the overall effects of sulfoxaflor were less than the catastrophic losses experienced by the colonies exposed to the reference toxicant. The effect of sulfoxaflor on brood development is considered inconclusive due to the limitations associated with the available studies (e.g. poor performance of control hives, lack of or short post-application observation period, lack of a concurrent control); however, no catastrophic effects are expected from the use of sulfoxaflor.

Colony Strength: When compared to controls, the effect of sulfoxaflor on colony strength applied at 3-32% of the US maximum proposed rate was either not apparent or modest at most. Sulfoxaflor applied to cotton foliage up to the maximum rate proposed in the US did not result in

an observable decline in mean colony strength by 17 days after the first application, when compared to colonies assessed 3 days prior to application.

IV. Proposed Regulatory Decision

The Agency is proposing to conditionally grant the registration of the new active ingredient, sulfoxaflor, formulated as a technical product and two end use products, under section 3(c)(7)(C) of the Federal Insecticide, Fungicide, and Rodenticide Act for the following uses: barley, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables, low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, root and tuber vegetables, small fruit vine climbing (except fuzzy kiwifruit), soybean, stone fruit, succulent, edible podded and dry beans, tree nuts, triticale, turfgrass, watercress, and wheat. The Agency has determined that, while it is necessary to condition this registration on a newly imposed data requirement (see IV.A below), the registration of these uses during the time period it takes to meet that data requirement will not cause any unreasonable adverse effect on the environment and is in the public interest. Restrictions on the use rates and patterns have been imposed to address the uncertain risk to bees; the crop-specific changes include decreasing the maximum single application rates from 0.133 to 0.09 lbs ai/acre, limiting application window or number of applications during bloom, and increasing the minimum spray interval (see section IV.C below).

As required by FIFRA, the Agency published a notice of receipt (NOR) of applications in the *Federal Register (December 22, 2010)* to grant the registration of one technical and two end use sulfoxaflor products. Five comments were received; all expressed support for the registration of sulfoxaflor. Two comments, provided by the National Cotton Council of America and a cotton farmer, expressed interest in using sulfoxaflor to control the tarnished plant bug. The other comments provided by university extension entomologists and the Florida Fruit and Vegetable Association indicated that sulfoxaflor would be useful as an alternative to currently registered pesticides. All comments can be found in docket EPA-HQ-OPP-2010-0889.

A. Data Requirements

The toxicology database for sulfoxaflor is complete, and the environmental fate database is adequate for a risk assessment.

Data on the effects of sulfoxaflor on pollinators indicate that adult bee mortality is short-lived, and the data do not show a positive indication of long term detrimental effects on brood. Although the six semi-field studies previously submitted provided useful data for assessing the effects of sulfoxaflor on bees, there is no conclusive evidence to rule out long-term more subtle brood impacts, and therefore as a condition of registration, the Agency is proposing to require the submission of:

(1) a Tier 2 semi-field study for assessing impacts on honey bee colony strength and brood development in accordance with OECD-established test guidelines;

(2) an additional residue study to assess the nature and magnitude of sulfoxaflor residues on a pollinator-attractive crop (e.g. canola).

These data are expected to resolve any residual uncertainty on the potential effects of sulfoxaflor applications on brood development and long-term colony health at the maximum application rate initially proposed by the registrant in the US (0.133 lbs ai/acre) and will determine whether this requested rate can be allowed in the future. Data currently on file indicate that sulfoxaflor applications will not result in a catastrophic loss to brood during the time period required for the conditional studies to be performed and assessed. Until the submission and determined acceptability of the above conditional data, a combination of additional crop-specific mitigation, including a decrease in the maximum single application rate (0.09 lbs ai/acre instead of the requested 0.133 lbs ai/acre) and/or an increase in minimum spray intervals are being proposed to reduce exposure to bees. This can be found in section IV.C below.

B. Public Interest

Sulfoxaflor has a unique mode of action which is not found in other insecticides, and it is the only chemical in its Insecticide Resistance Action Committee (IRAC) subgroup C within the group 4 nicotinic acetylcholine receptor agonists. Furthermore, there is a lack of cross-resistance between sulfoxaflor and the neonicotinoids (IRAC group 4A). Registration of sulfoxaflor will provide growers with a valuable new pest management tool to kill a broad spectrum of piercing/sucking insects, including species which are difficult to control. For example, in 2012 Emergency Exemption requests were submitted by Arkansas, Mississippi, Tennessee, and Louisiana for use of unregistered sulfoxaflor on cotton to control the tarnished plant bug, an insect that has developed resistance to registered alternative pesticides. The Agency concluded that an emergency condition existed in these states; in order to avert a significant economic loss by the affected growers, the Agency granted the requested emergency use of sulfoxaflor.

C. Labeling Requirements

Based on the human health and ecological risk assessments, the applicant has revised the draft end use product labels. The revised draft labels can be found in docket EPA-HQ-OPP-2010-0889. A summary of the changes to the new draft end use product labels from the draft labels initially submitted for registration are below.

1.) For 62719-AEG, the Restricted Entry Interval (REI) was changed from 24 to 12 hours, as identified in the human health risk assessment and supported by the submitted data.

2.) For both end use products, the Environmental Hazards section was revised to the following:
"This product is highly toxic to bees exposed through contact during spraying and while spray droplets are still wet. This product may be toxic to bees exposed to treated foliage for up to 3 hours following application. Toxicity is reduced when spray droplets are dry.

Risk to managed bees and native pollinators from contact with pesticide spray or residues can be minimized when applications are made before 7:00 am or after 7:00 pm local time. Refer to the Directions for Use for crop specific restrictions to protect pollinators. Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwaters."

3) To provide additional crop-specific pollinator protection mitigation, both end use labels have been revised as follows:

i) The statement "Do not apply during bloom" has been added to the directions for use for barley, wheat, and triticale; *Brassica* leafy vegetables (Crop Group 5); bulb vegetables (Crop Group 3-07); leafy vegetables except *Brassica* (Crop Group 4); leaves of root and tuber vegetables (Crop Group 2); root and tuber vegetables (Crop Group 1A and 1B); turfgrass; and watercress.

ii) The statement "Do not apply [this product] 3 days prior to bloom, during bloom, or until petal fall" has been added to the directions for use for canola; small fruit vine climbing (except fuzzy kiwi fruit) (Subgroup 13-07F); low growing berry (Subgroup 13-07G) except strawberry; pistachios; pome fruit (Crop Group 11); stone fruit (Crop Group 12); tree nuts (Crop Group 14).

iii) The statement "Do not make more than one application of 5.75 fl oz acre (0.09 lb ai) 3 days prior to bloom, during bloom, or until petal fall" has been added to the directions for use for citrus.

iv) The statement "Do not make more than 0.023 oz/gal or 2.25 oz/100 gal (0.071 lb ai/acre) during bloom" has been added to the directions for use for ornamentals.

v) The statement "No more than two applications may be made to soybean forage" has been added to the directions for use for soybeans.

vi) The maximum single application rate has been reduced from 0.133 lbs ai/acre to 0.09 lbs ai/acre for the following crops: citrus (Crop Group 10); ornamentals; pistachio; pome fruit (Crop Group 11); stone fruit (Crop Group 12); tree nuts (Crop Group 14); and turfgrass.

vii) The maximum single application rate has been reduced from 0.09 lbs ai/acre to 0.069 lbs ai/acre for the following crops: cotton, cucurbits (Crop Group 9); fruiting vegetables (Crop Group 8); okra; potatoes (Crop Group 1C and 1D); strawberry; soybean; and succulent, edible podded and dry beans.

viii) The minimum treatment interval has been increased from 7 days to 14 days for the following crops: citrus; ornamentals; potatoes (Crop Group 1C and 1D); soybean; and succulent, edible podded and dry beans.

Registration of the New Active Ingredient Sulfoxaflor for Use on Multiple Commodities, Turfgrass and Ornamentals

Approved by: Daniel J. Rosenblatt (for)

Lois Rossi, Director
Registration Division

Date: 5/8/2013

Registration Decision for the New Active Ingredient Sulfoxaflor

Regulatory Rationale

The Agency is unconditionally granting the registration of the new active ingredient sulfoxaflor, formulated as a technical product and two end use products, under section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act. The uses being granted are barley, *Brassica* (cole) leafy vegetables, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables (except *Brassica*), low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, root and tuber vegetables, potatoes, small fruit vine climbing (except fuzzy kiwifruit), strawberry, soybean, stone fruit, succulent, edible podded and dry beans, tree nuts, triticale, turfgrass (commercial sodfarms and grass grown for seed), watercress, and wheat.

I. Chemical Information

Chemical Name: sulfoxaflor; cyanamide, N-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl] λ^4-sulfanylidene]

EPA PC Code: 005210

Chemical Abstracts Service (CAS) Number: 946578-00-3

IRAC MoA Classification: Group 4C: Nicotinic acetylcholine receptor agonists, sulfoxamines

Mode of Action: Sulfoxaflor is an insecticide that acts through a unique interaction with the nicotinic acetylcholine receptor in insects. While sulfoxaflor acts on the same receptor as the neonicotinoids, it is classified as its own subgroup (4C). It is an agonist of the nicotinic acetylcholine receptor (nAChR) and exhibits excitatory responses including tremors, followed by paralysis and mortality in target insects. The structure of sulfoxaflor makes it stable in the presence of a monooxygenase enzyme that was shown to degrade a variety of neonicotinoids in IRAC Group 4A, resulting in a lack of cross-resistance demonstrated in laboratory experiments.

Registrant: DOW AgroSciences LLC

Proposed Products: Sulfoxaflor is being registered as EPA Reg. 62719-631 (Sulfoxaflor Technical), 62719-625 (Transform WG), and EPA Reg. 62719-623 (Closer SC).

Methods of application include aerial and ground broadcast, in addition to chemigation for potato. Maximum annual application rates range from 0.046-0.266 lbs a.i./A/year.

II. Human Health Risk

A summary of the human health effects and risk of sulfoxaflor as assessed in the Agency document entitled "*Sulfoxaflor—New Active Ingredient Human Health Risk Assessment of Uses on Numerous Crops*" is provided below.

A. Summary of Toxicological Effects

Sulfoxaflor is the only member of a new class of insecticides and is a highly efficacious activator of the nicotinic acetylcholine receptor (nAChR) in insects. Toxicity and mechanistic studies in rats, rabbits, dogs and mice indicate that sulfoxaflor is an activator of the mammalian nAChR as well, but to a much lesser degree and in a species-specific manner. The database of guideline toxicity studies indicates that the nervous system and liver are the target organ systems, resulting in developmental toxicity, hepatotoxicity, and other apical effects.

Developmental/offspring toxicity, manifested as skeletal abnormalities and neonatal deaths, was observed in rats only. The skeletal abnormalities, including forelimb flexure, bent clavicles, and hindlimb rotation, likely resulted from skeletal muscle contraction due to activation of the skeletal muscle nAChR *in utero*. Contraction of the diaphragm, also related to skeletal muscle nAChR activation, prevented normal breathing in neonates and resulted in increased mortality in the reproduction studies. Furthermore, targeted studies indicate that offspring effects are dependent upon *in utero* exposure to sulfoxaflor. The skeletal abnormalities were observed at high doses in the developmental and reproduction studies while decreased neonatal survival was observed at slightly lower levels (e.g., mid- and high-dose animals).

Exposure to sulfoxaflor and its major metabolites resulted in hepatotoxicity in several guideline studies. For example, sulfoxaflor caused liver weight and enzyme changes, hypertrophy, proliferation, and tumors in subchronic and chronic studies. Short-term studies with metabolites resulted in similar liver effects. For sulfoxaflor, hepatoxicity occurred at lower doses in long-term studies compared to short-term studies.

In addition to the developmental and hepatic effects, treatment with sulfoxaflor resulted in decreased food consumption and body weight as well as changes in the male reproductive system. Decreased body weight, body weight changes, and food consumption were observed during the first few days of several oral studies at the mid- and high-dose levels. As a result of decreased feeding early in the studies, body weights were typically lower in the mid- and high-dose groups compared to the controls, although the differences were not generally statistically significant. Decreased palatability is a likely contributor to this effect as body weight decreases were often observed at study initiation but were comparable to control animals within several weeks.

Effects in the male reproductive organs were observed in the chronic/carcinogenicity study in rats that included increased testicular and epididymal weights, atrophy of seminiferous tubules, and decreased secretory material in the coagulating glands, prostate, and seminal vesicles. Additionally, there was an increased incidence of interstitial cell (Leydig cell) tumors. The Leydig cell tumors observed after exposure to sulfoxaflor are not considered treatment related due to the lack of dose response, the lack of statistical significance for the combined tumors (unilateral and bilateral), and the high background rates for this tumor type in F344 rats. The primary effects on male reproductive organs are considered secondary to the loss of normal testicular function due to the size of the interstitial cell (Leydig Cell) adenomas. Consequently, the secondary effects to the male reproductive organs are also not considered treatment related.

Clinical indications of neurotoxicity were only observed at high doses in the acute neurotoxicity study in rats. At the highest dose tested, muscle tremors and twitches, convulsions, hindlimb splaying, increased lacrimation and salivation, decreased pupil size and response to touch, gait abnormalities and decreased rectal temperature were observed. Decreased motor activity was also observed in the mid- and high-dose groups. Since the neurotoxicity was observed only at a very high dose and many of the effects are not consistent with the perturbation of the nicotinic receptor system (e.g., salivation, lacrimation, and pupil response), it is unlikely that these effects are due to activation of the nAChR.

Finally, tumors were observed in chronic rat and mouse studies. In rats, significant increases in the incidence of hepatocellular adenomas and combined adenomas and/or carcinomas in the high-dose males were observed when compared to controls. In mice, there were significant increases in hepatocellular adenomas, carcinomas, and combined adenomas and/or carcinomas in high dose males when compared to controls. In female mice, there was an increase in the incidences of carcinomas at the high dose. Although this increase did not reach statistical significance, the incidences exceeded the historical control range for this tumor type and were corroborated with the presence of non-neoplastic lesions at this dose. EPA determined that the liver tumors in mice were treatment-related. Using data from several mechanistic studies, EPA also determined that the liver effects in mice are non-linear (threshold) in their mode of action (MoA) and the MoA for the liver tumors is consistent with a constitutive androstane receptor (CAR) mediated, mitogenic mode-of-action. Leydig cell tumors were also observed in the high-dose group of male rates, but it was determined that the tumors were not related to treatment. There was also a significant increase in the incidence of preputial gland tumors in male rats in the high-dose group. Marginal increases were also observed in the low- and mid-dose groups; however, the incident values for these groups were within the range of historical control values. Preputial gland tumors are not commonly diagnosed in bioassay studies. The available data were inadequate to draw confident conclusions regarding this response due to the small sample size and lack of histopathology data on all animals. Thus, it was not possible to determine whether the preputial gland tumors are due to treatment. If the response is positive, this would be an unusual finding. Because the tumors could not be discounted, they were used in the suggestive classification.

Based on the weight of evidence, including mode-of-action data, the EPA determined that there is "Suggestive Evidence of Carcinogenic Potential" for sulfoxaflor, based on the preputial gland tumor response seen in rats. Suggestive evidence of carcinogenicity means there is some limited potential for carcinogenic effects but the evidence is judged not sufficient for linear quantification of cancer risk in humans as the nature of the data generally does not support one. The data here do not support a linear quantification of the cancer risk because the treatment-related liver tumors in mice are produced by a mode-of-action subject to a threshold. In addition, the Leydig cell tumors were not treatment-related, and the preputial gland tumors only occurred at the high dose in one sex of one species; therefore, EPA concluded that the evidence of potential carcinogenicity was weak and that that quantification of risk using a non-linear approach (i.e., reference dose (RfD) will adequately account for all chronic toxicity, including any potential carcinogenic effects, that could result from exposure to sulfoxaflor. The current NOAEL of 5.13 mg/kg/day used for chronic dietary risk assessment is significantly (4x) lower than the dose where tumors were observed $\geq$ 21.3 mg/kg/day.

In addition, EPA determined there was sufficient evidence to support a developmental mode-of-action (i.e., activation of the nAChR) accounting for the skeletal abnormalities and increased mortality observed in the rat. Furthermore, there was sufficient evidence to support that rats are uniquely sensitive to these developmental effects, informing interspecies uncertainty. Although the database indicates that the developmental effects are unlikely to be relevant to humans, the effects will be considered as relevant to humans unless additional information to the contrary is provided. Data are sufficient to support reducing the interspecies uncertainty factor to 3X for the developmental effects.

B. FQPA Safety Factor

EPA has determined that reliable data show the safety of infants and children would be adequately protected if the FQPA SF for sulfoxaflor were reduced to 1x. That decision is based on the following findings:

1. The toxicity database for sulfoxaflor is complete.

2. There is a low level of uncertainty regarding the neurotoxic effects observed in the database because the effects are well characterized, the dose-response curve for these effects is well characterized, and clear NOAELs have been identified. As the doses selected for risk assessment are protective for the neurotoxic effects and are coupled with appropriate safety factors, there is a low level of concern for neurotoxicity.

3. Although there is evidence of quantitative susceptibility in the DNT study, based on decreased survival of offspring up to postnatal day 4, the endpoints and doses selected for risk assessment are protective for these effects. Further, EPA's degree of concern for human susceptibility is reduced based on the special studies submitted in support of the mode of action.

4. There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessments were performed based on 100% CT and either maximum or average residue levels from field trials. EPA made conservative (protective) assumptions in the ground and surface water modeling used to assess exposure to sulfoxaflor in drinking water. Although some refinements were used in the exposure assessment, the dietary and drinking water assessments will still result in the upper-bound estimates of exposure.

C. Toxicological End Points and Doses Used in the Human Health Risk Assessment

1. Acute: EPA established an acute reference dose (aRfD) and an Acute Population Adjusted Dose (aPAD) for sulfoxaflor for the general population, which included groundwater exposure to the metabolites of sulfoxaflor, of 0.25 mg/kg body wt/day, based on the "No Observable Effects Level" (NOAEL) of 25 mg/kg body weight/day from the acute neurotoxicity study in rats and an uncertainty factor of 100. In this study, decreased motor activity was observed at the "lowest observed adverse effect level" (LOAEL) of 75 mg/kg body wt/day. EPA also established an

aRfD and an aPAD for sulfoxaflor for females 13-50 years of age, which included surface water exposure to the sulfoxaflor parent compound, of 0.06 mg/kg body wt/day, based on the "No Observable Effects Level" (NOAEL) of 1.8 mg/kg body weight/day from the developmental neurotoxicity study in rats and an uncertainty factor of 30. In this study, decreased neonatal survival (PND 0-4) was observed at the "lowest observed adverse effect level" (LOAEL) of 7.1 mg/kg body wt/day.

2. Chronic Dietary: EPA established a chronic reference dose (cRfD) and a Chronic Population Adjusted Dose (cPAD) for sulfoxaflor of 0.05 mg/kg body wt/day, based on the NOAEL of 5.13 mg/kg body wt/day from the chronic/carcinogenticty study in rats and an uncertainty factor of 100. In this study, liver effects were observed at the LOAEL of 21.3 mg/kg body wt/day. These effects include hypertrophy, fatty change, and increased blood cholesterol, liver weight, single cell necrosis, and macrophages.

3. Short- and Intermediate-Term Dermal and Inhalation: The same endpoint (toxic effect) and dose (NOAEL) were selected for assessing short- and intermediate-term dermal and inhalation exposure. EPA selected the NOAEL of 1.8 mg/kg body wt/day from the developmental neurotoxicity study based on decreased neonatal survival (PND 0-4) observed at the LOAEL of 7.1 mg/kg body wt/day. A dermal absorption factor of 2.4% and an inhalation absorption factor of 100% were used in the relevant exposure assessments.

The current risk metric for assessing short- and intermediate-term occupational exposure to sulfoxaflor is a margin of exposure (MOE) that is less than 30. At a baseline level of personal protective equipment (PPE), estimated occupational MOEs range from 80 to 4,700,000, and the vast majority of the estimates are greater than 300. All estimated occupational MOEs indicate that risks are below EPA's level of concern.

4. Cancer: EPA has classified sulfoxaflor as "Suggestive Evidence of Carcinogenic Potential" based on the preputial gland tumor response observed in rats. The Agency has determined that quantification of risk using a non-linear approach (i.e., reference dose (RfD)) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to sulfoxaflor.

D. Cumulative Effects

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not found sulfoxaflor to share a common mechanism of toxicity with any other substances, and sulfoxaflor does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has assumed that sulfoxaflor does not have a common mechanism of toxicity with other substances.

E. Aggregate Risk Assessment

1. Dietary (Food + Drinking Water) Risk:

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™ (v. 2.03), uses food consumption data from the U.S. Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. EPA has assumed 100% of crops covered by the registration request are treated with sulfoxaflor.

Acute Dietary Risk: The data used in the acute assessment reflect several refinements relative to a screening-level assessment. Maximum residue values from field trials were used rather than tolerance-level residue estimates. The field trials are designed to produce high-end residue levels in crops and although these values are less than the tolerance value, their use in risk assessment is considered to be very health protective. For crop groups, the residue values were translated from representative crops to the other crops in the group. For processed commodities, empirical processing factors were used for all commodities unless an empirical factor was not available, in which case the DEEM default estimate was used. Residue estimates for livestock were derived using maximum observed residues in the cattle and hen feeding studies.

Acute dietary risk estimates range from 4% to 16% of the acute population-adjusted dose (aPAD), with the highest risk estimates being for children 1-2 years old and females 13-49 years old. Generally, EPA is concerned when exposure estimates exceed 100% of the population-adjusted dose (PAD). Even with the conservatisms in the assessment, acute dietary risk estimates are below EPA's level of concern.

Chronic Dietary Risk: For the chronic assessment, the same refinements were made as those described for the acute assessment, with two exceptions: (1) average residue levels from crop field trials were used rather than maximum values and (2) average residues from feeding studies, rather than maximum values, were used to derive residue estimates for livestock commodities. The use of average residue values in chronic risk assessment is appropriate since residue levels in foods would be averaged over the long-term consumption patterns reflective of chronic assessments. As with the acute assessment, the residues from crop field trials are considered to be high-end values with built-in conservatism, even when average residue values are used.

Chronic dietary risk estimates range from 5% to 18% of the chronic population-adjusted dose (cPAD) with the highest risk estimate estimated for infants. All of the risk estimates are below EPA's level of concern.

2. Residential Risk:

Residential exposures and risk were not assessed because the proposed uses of sulfoxaflor do not involve applications by homeowners or commercial applicators in residential settings at this time.

3. Aggregate Risk:

There are no residential uses for sulfoxaflor; therefore the aggregate exposure and risk assessments include acute and chronic dietary (food and water) only and are reported above. There are no aggregate risk concerns for the proposed new uses of sulfoxaflor.

F. Occupational Risk Assessment

1. Handler Exposure and Risk:

Dermal and inhalation occupational handler scenarios for the proposed uses resulted in estimated MOEs that are greater than 30 and therefore are not of concern. This was determined at the baseline level of PPE (i.e., baseline clothing, no gloves, and no respirator) and engineering controls (enclosed cockpit) for aerial applications.

2. Occupational Postapplication Exposure and Risk:

Occupational workers who enter treated fields to perform post-application activities such as hand weeding and scouting may be exposed dermally to sulfoxaflor residues. Based on the use pattern, workers may be exposed to short- and intermediate-term exposure durations. Post-application dermal exposure and risk estimates resulted in MOEs greater than 30 and are not of concern.

A quantitative post-application inhalation exposure assessment was not performed for sulfoxaflor at this time primarily because it has a low vapor pressure and it is applied at low application rates. Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational handlers. This assessment resulted in risk estimates that did not exceed EPA's level of concern at baseline inhalation PPE. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios. Furthermore, the Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

III. Environmental Risk

A summary of the environmental fate and ecological effects and risks of sulfoxaflor as assessed in the Agency document entitled *"Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration"* is provided below.

A. Environmental Fate

Sulfoxaflor has a low potential for volatilization from dry and wet surfaces (vapor pressure= 1.9×10^{-8} torr and Henry's Law constant= 1.2×10^{-11} atm m^3 $mole^{-1}$, respectively at 25 °C). The chemical is characterized by a water solubility ranging from 550 to 1,380 ppm. Partitioning coefficient of sulfoxaflor from octanol to water (K_{ow}= 6; Log K_{ow}= 0.802) suggests low potential for bioaccumulation in aquatic organisms such as fish.

Sulfoxaflor reaching the soil system is subjected to rapid aerobic bio-degradation ($t_{½}$ <1 day) while that reaching foliage may enter the plant tissue and persist much longer. Sulfoxaflor has shown to be stable to hydrolysis/photolysis on soil and in aquatic environments. In field studies, sulfoxaflor has shown similar vulnerability to aerobic bio-degradation in nine out of ten terrestrial field dissipation studies on bare-ground/cropped plots (half-lives were <2 days in nine cropped/bare soils in CA, FL, ND, ON and TX and was 8 days in one bare ground soil in TX).

The chemical is characterized by very high to high mobility (K_{foc} ranged from 11-72 mL g^{-1}). Rapid soil degradation is expected to limit chemical amounts that may potentially leach and contaminate ground water. Contamination of groundwater by sulfoxaflor will only be expected when excessive rain occurs within a few days of multiple applications in vulnerable sandy soils. Contamination of surface water by sulfoxaflor is expected to be mainly related to drift and very little due to run-off. This is because drifted sulfoxaflor that reaches aquatic systems is expected to persist while that reaching the soil system is expected to degrade quickly with slight chance for it to run-off.

In contrast to sulfoxaflor parent, the major degradate X-474 and two other degradates (X-540 and X-457) are expected to be highly persistent in aerobic soil/aquatic systems. Adsorption data for these degradates indicate that they can be characterized by very high to high mobility for X-474 (K_{foc} ranged from 7-68 mL g^{-1}) and very high mobility for X-457 and X-540 (K_{foc} ranged from 2-44 mL g^{-1} for X-457 and K_{foc} ranged from 1-25 mL g^{-1} for X-540). Both surface and ground water contamination is expected from these three degradates following leaching drift/run-off events. The major degradate X-474 is expected to dominate the exposure resulting from use of sulfoxaflor.

B. Ecological Risk

Ecological risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of integrating the results of exposure and ecotoxicity data is called the quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic (RQ = Exposure/Toxicity). RQs are then compared to EPA's levels of concern (LOCs). The LOCs are criteria used by the Agency to indicate potential risk to non-target organisms. The criteria indicate whether a pesticide, when used as directed, has the potential to cause adverse effects to non-target organisms. EPA notes that the initial ecological risk assessment was performed using the higher rates proposed by the registrant, and the proposed decision reflected conclusions made based on the higher rates. The information presented below reflects the mitigated lower rates.

1. Aquatic Organisms

Fish: Sulfoxaflor is classified as practically non-toxic to freshwater and saltwater fish on an acute exposure basis. As a result, maximum acute and chronic RQ values for freshwater and saltwater fish determined with the crop exposure scenario producing the highest aquatic estimate exposure concentrations (EECs), NC Cotton, are below the applicable listed and non-listed LOC values.

Invertebrates: Maximum acute RQ values for freshwater invertebrates are three orders of magnitude below the acute risk to listed species LOC, while that for saltwater invertebrates marginally exceeds (RQ=0.08) the acute risk to listed species LOC of 0.05.
For saltwater invertebrates, maximum acute RQ values based on refined EECs which include the toxicological residues of concern (parent + X-540) are well below LOCs for non-listed and listed species. Maximum chronic RQ values do not exceed the chronic risk LOC (1.0) for either freshwater or saltwater invertebrates.

For estimating acute risks to benthic invertebrates, RQs were determined using peak pore water EECs divided by the lowest acute toxicity endpoint for fresh and saltwater water column invertebrates, since acute toxicity data were not available from sediment toxicity studies. For estimating chronic risks to benthic invertebrates, RQs were determined by dividing the highest 21-d average EEC in pore water by the lowest pore water NOAEC obtained for the midge (freshwater) and water column exposure NOAEC for mysid shrimp. Based on these comparisons, acute or chronic risk LOCs were not exceeded for listed and non-listed species of freshwater benthic invertebrates. For saltwater benthic invertebrates, refined RQ values using the toxicological residues of concern (parent + X-540) are well below acute and chronic risk LOCs for non-listed and listed species.

Plants: None of the risk quotients calculated for vascular and non-vascular aquatic plants using the crop exposure scenario with the highest acute and chronic EECs in surface water (NC cotton) exceed the LOC for listed or non-listed aquatic plant species.

2. Terrestrial Organisms

Mammals: Maximum acute mammalian RQ values are all below 0.1 which indicates a low acute risk potential to listed and non-listed mammals consuming the modeled forage items.

Potential chronic risks to mammals are derived using a dietary-based NOAEL of 100 ppm from a 2-generation reproduction study with the rat and EECs for the crop exposure scenario yielding the maximum residues on forage items (2 x 0.0.086 lb ai/A). The chronic dietary-based RQ values range from 0.02 (fruits, pods, seeds, large insects) to 0.35 (short grass). Since these chronic RQ values are all below the chronic risk LOC of 1.0, the potential for chronic risks to mammals based on a dietary approach is considered low.

Potential chronic risks to mammals are also evaluated using a dose-based approach which relies on a NOAEL of 6.07 mg a.i./kg bw/d from the same 2-generation toxicity rat study. This dose-based NOAEL is adjusted to account for different size classes of mammals. These adjusted values are used to interpret the dose-based EECs calculated for the same mammalian size classes. The overall range in chronic RQ values is from 0.01 to 2.5, and the potential for chronic risks to mammals is identified for all crop scenarios for at least one dietary category.

Birds: For sulfoxaflor, avian dose-based acute RQs are based on the zebra finch acute oral toxicity data (LD_{50} > 80 mg a.i./kg bw) which reflects the concentration above which dose-dependent effects of regurgitation were observed. Thus, a value of 80 mg a.i./kg bw is used as a

conservative screen for acute risks to birds. Acute dose-based RQ values are based on LD_{50} values adjusted differences in body weight for birds (20, 100, 1000g) (adjusted LD_{50} =86.4, 110 and 155 mg a.i./kg bw, respectively) and modeled acute dose-based EECs for various use scenarios and diet categories, and a sulfoxaflor-specific foliar DT_{50} of 12.3 days. The overall range in avian acute RQ values is from <0.01 to 0.5, and the potential for acute risks to birds (including reptiles and terrestrial-phase amphibians) is identified for all crop scenarios for at least one dietary category. However, this acute risk concern is subject to considerable uncertainty because a definitive LD_{50} value could not be determined due to regurgitation of administered dose and the close proximity of the RQ values to the listed and non-listed species acute risk LOCs (0.1 and 0.5, respectively). The actual avian acute LD_{50} would be expected to be higher than 80 mg a.i./kg bw if a definitive LD_{50} had been determined. A higher LD_{50} would result in lower acute risk or possibly no acute risk. No avian subacute acute risk is identified with the dietary-based approach, as RQ values are all well below the acute risk to listed species LOC of 0.1. Chronic dietary-based RQs range from 0.02 to 0.27, thus indicating a low potential for chronic risks to birds.

Plants: The NOAEC values from seedling emergence and vegetative vigor toxicity tests of terrestrial plants are above the maximum single application rate that was assessed of 0.133 lb ai/A. Therefore, a low potential for risk to listed and non-listed terrestrial plants is expected based on the proposed use profile for sulfoxaflor. Further the maximum single application rate was lowered after this assessment was conducted.

Bees: Sulfoxaflor is classified as very highly toxic with acute oral and contact LD_{50} values of 0.05 and 0.13 µg a.i./bee, respectively, for adult honey bees (*Apis mellifera*). For larvae, a 7-d oral LD_{50} of >0.2 µg a.i./bee was determined (45% mortality occurred at the highest treatment of 0.2 µg a.i./bee). Sulfoxaflor's primary metabolite (X-474) is practically non-toxic to the honey bee. The acute oral toxicity of sulfoxaflor to adult bumble bees (*Bombus terrestris*) is similar to the honey bee, whereas its acute contact toxicity is about 20X less toxic for the bumble bee. Sulfoxaflor did not demonstrate substantial residual toxicity to honey bees exposed via treated and aged alfalfa (*i.e.*, mortality was ≤15% at maximum application rates).

For the initial Tier 1 screen, the dietary and contact exposure routes are considered. Acute risks to bees from contact exposure were determined based arthropod residues estimated from the Agency's T-REX model (v. 1.5.1) and the range of application sulfoxaflor rates (0.023 to 0.086 lb a.i./A). Acute contact RQ values range from 0.5 to 1.8, which exceeds the acute risk level of concern for bees (0.4). For generating oral RQs, dietary-based exposure values are compared to oral toxicity data for larvae and adult worker bees while contact exposure values are compared to acute contact toxicity data for adult worker bees.

The initial screening-level RQs exceeded the proposed LOC of 0.4 for adult (oral and contact) exposures. Additional refinements of the Tier 1 exposure estimates were conducted using chemical-specific data on residues in pollen and nectar. The total estimated oral dose to bees was based on the maximum reported residues of sulfoxaflor in pollen and nectar obtained from the various residue studies for crops treated up to the current maximum application rate of 0.086 lb a.i./A (6.6 and 0.126 ppm respectively). With these maximum reported residue values, the total oral dose to various castes of adult and larval bees was then estimated using caste-specific

consumption rates of pollen and nectar. For each bee caste, the total oral dose was then divided by the applicable acute oral LD50 (0.0515 µg ai/bee for adult workers and >0.2 µg ai/bee for larvae, respectively) to derive the acute RQ values. The resulting oral, acute RQs range from <0.1 to < 0.3 (for bee larvae) and 0.1 to 1.5 (for adult bees). The upper bound of the oral acute RQs for larvae do not exceed the acute risk LOC of 0.4, but the RQs for the highest exposed castes of adult bees do exceed the acute risk LOC. This indicates that acute risk to honey bee colonies cannot be precluded and analysis of effects at the whole hive level is warranted (Tier 2).

It is important to note that the Tier 1 refinement is based on the maximum reported residues of sulfoxaflor in pollen and nectar obtained from the available residue studies. Based on the estimated median consumption rates of pollen and nectar, it is clear that the oral exposure of adult and larval honey bees is dominated by the consumption of nectar, with more than 90% of the total consumed food source represented by nectar. Given the importance of nectar as a source of food and potential contaminant exposure, the concentration in nectar that would meet or exceed the proposed acute risk LOC of 0.4 was determined. Based on the acute LD50 of 0.0515 µg a.i./bee and a consumption rate of 292 mg/d for adult nectar foragers, a concentration of > 0.07 ppm in nectar would result in an acute oral RQ that meets or exceeds the proposed LOC of 0.4. The adult nectar forager caste was chosen because it has the highest estimated nectar consumption rate among the various castes assessed. A comparison of each of the 66 reported residues of sulfoxaflor in cotton nectar reveals that only 2 values (3%) exceeded the 0.07 ppm LOC-based threshold. These nectar residue values are within a factor of two of the 0.07 ppm residue threshold corresponding to the acute risk LOC. The vast majority of sulfoxaflor residues in nectar (78%) are less than half the 0.07 ppm LOC-based threshold in nectar. Similarly for pollen, only 2 residue values in plant pollen and 1 residue value in forager bee-collected pollen exceed the acute risk residue threshold (2.5 ppm for nurse bees) based on the cotton study. These residue values represent 3% and 2% of the measured residues in plant pollen and forager bee-collected pollen, respectively. This distribution of pollen and nectar residue values from the cotton study likely reflects the dissipation and degradation of sulfoxaflor from plant tissue. Specifically, most of the dissipation half life values for sulfoxaflor in pollen and nectar from the cotton study were 3 days or less.

A detailed analysis of six available Tier 2 semi-field (tunnel) studies was conducted in order to confirm or refute the risks identified from the Tier 1 assessment on honey bees. Importantly, results from the Tier 2 semi-field (tunnel) studies represent 'worst case' exposure conditions while bees housed in tunnels because pesticide is applied when bees are present (contact exposure) and bees are forced to feed on treated crop (oral exposure). These six semi-field studies used application rates ranging from 4 to 150% of the single maximum application rate of 0.086 lb a.i./A currently proposed for the US. Two of the six semi-field studies included the current single maximum application rate in the study design.

Direct Effects on Bees: Direct effects on bees are those that result directly from interception of spray droplets or dermal contact with and ingestion of foliar residues. The Agency has mitigated risk to pollinators through rate reductions, increased minimum spray intervals, and bloom application restrictions, as listed below. Results from the Tier 2 semi-field studies suggest that at the application rates used (4-150%% of US maximum), the direct effects of sulfoxaflor on adult forager bee mortality, flight activity and the occurrence of behavioral abnormalities is relatively

short-lived, lasting 3 days or less. In contrast, the reference toxicant used in these studies indicated much greater, sustained mortality over the duration bees were housed in the tunnels.

Brood Development: In the two submitted studies most appropriate to determine brood effects, a large increase in brood termination rate (i.e., larval mortality) was observed for the reference toxicant (fenoxycarb), compared to the control for these two studies. This increase in brood termination rate caused by the reference toxicant indicates that despite the high larval mortality in control hives, a major catastrophic impact on brood could be detected in hives treated with the reference toxicant. Although uncertain due to high mortality of larvae in controls, the effects of sulfoxaflor applications on brood development were similar to that of the controls. These results suggest that the study design allows for the detection of catastrophic losses to the brood, as seen in the hives exposed to fenoxycarb, and that the overall effects of sulfoxaflor were less than the catastrophic losses experienced by the colonies exposed to the reference toxicant. The effect of sulfoxaflor on brood development is considered inconclusive due to the limitations associated with the available studies (e.g. poor performance of control hives, lack of or short post-application observation period, lack of a concurrent control); however, no catastrophic effects are expected from the use of sulfoxaflor.

Colony Strength: The colony strength of hives exposed to crops treated with sulfoxaflor at 4-150% of the proposed US maximum rate was similar to control or pre-exposure hives in four studies where this endpoint could be evaluated. In one of these studies, a slight reduction in hive strength occurred but this was inconsistent over the course of measurements following exposure. Sulfoxaflor applied to cotton foliage up to the 0.134 lb a.i./A (150% of the current maximum single rate) did not result in an observable decline in mean colony strength by 17 days after the first application, when compared to colonies assessed 3 days prior to application.

A limitation of the submitted tunnel studies is that their design and did not enable evaluation of long-term effects after colonies were removed from the tunnels at the highest application rate. Long-term effects were evaluated at the lower application rates (0.043 lb a.i./A and below) with no long-term effects on colony strength indicated. Therefore, while the current information base does not indicate that long-term effects of sulfoxaflor on colonies are likely at the current application rates, the design of the Tier 2 studies does not enable the potential for long-term effects to be discounted completely.

IV. Regulatory Decision

The Agency is unconditionally granting the registration of the new active ingredient, sulfoxaflor, formulated as a technical product and two end use products, under section 3(c)(5) of FIFRA. Sulfoxaflor is being registered for the following uses: barley, *Brassica* (cole) leafy vegetables, bulb vegetables, canola (rapeseed), citrus, cotton, cucurbit vegetables, fruiting vegetables, leafy vegetables, root and tuber vegetables, low growing berry, okra, ornamentals (herbaceous and woody), pistachio, pome fruits, potatoes, small fruit vine climbing, strawberry, soybean, stone fruit, succulent, edible podded and dry beans, tree nuts, triticale, turfgrass, watercress, and wheat. EPA has concluded that the registration of these uses, with application rate reductions and other use restrictions, will not cause unreasonable adverse effects on humans or the environment.

EPA announced a proposed decision for a conditional registration of sulfoxaflor on January 14, 2013, and held public comment period for 30 days. The Agency received 364 comments as well as a letter writing campaign and two comment letters totaling >10,000 signatures. Commenters in favor of registration included multiple grower associations on behalf of large numbers of growers, individual growers, entomologists and researchers in academia, USDA's Interregional Research Project No. 4, and agricultural consultants. These commenters indicated that there are resistance issues with currently registered pesticides and that sulfoxaflor would be an alternative to organophosphates, pyrethroids, and neonicotinoids. They also cited specific examples of where sulfoxaflor has shown to be less harsh on beneficial insects. They noted that it is very efficacious against a number of hard-to-kill pests including the woolly apple aphid and the tarnished plant bug and that it does not result in flare-ups of aphids. Additionally, they confirmed that no adverse incidents were reported under the emergency exemption use on cotton in 2012. They expect sulfoxaflor's new mode of action would be beneficial to IPM programs and would replace older, more toxic chemistries.

Commenters against registration of sulfoxaflor included Beyond Pesticides, Center for Food Safety, several pollinator protection groups, beekeepers, and members of the general public. While the commenters noted a number of concerns, the main focus was the belief that sulfoxaflor registration would pose a risk to bees and that the pollinator studies were incomplete or inconclusive. While the comments identified serious concerns related to the health of bee populations in the United States, none of these comments pointed to any data to support the opinion that registration of sulfoxaflor will pose a grave risk to bees. Instead, the comments generally relied on statements the Agency has made with respect to sulfoxaflor, or suggested that pesticides can pose risks to bees and that the Agency should not allow yet another pesticide to threaten bees.

The Agency's response to the substantive comments can be found in docket # EPA-HQ-OPP-2010-0889.

EPA's January 14, 2013 proposal for a conditional registration under FIFRA 3(c)(7)(C) was intended to take comment on requiring data to resolve any residual uncertainty on the potential effects of sulfoxaflor on brood development and long-term colony health at the maximum application rate originally proposed by the registrant and to determine whether this rate can be allowed in the future. After review of the public comments and further consideration of the database, EPA has concluded that an unconditional registration of sulfoxaflor, with lowered application rates and other mitigation (described below) is supported by the available data and therefore the appropriate regulatory decision.

A. Risk Benefit Determination

EPA conducted an extensive analysis of sulfoxaflor in collaboration with counterpart agencies in Australia and Canada. The Pest Management Regulatory Agency in Canada has already granted registration of sulfoxaflor; the Australian Pesticides and Veterinary Medicines Authority has indicated that they intend to do so as well. EPA believes that the risk benefit standard has been met for granting the registration of sulfoxaflor in the US.

As required by FIFRA, the Agency published a Notice of Receipt (NOR) of applications in the *Federal Register (December 22, 2010)* to grant the registration of one technical and two end use sulfoxaflor products. All comments received in response to the Notice of Receipt were in favor of granting the registration of sulfoxaflor products. No comments objecting to the registration were received.

Sulfoxaflor has already met the FIFRA Section 18 requirements to address an emergency condition, i.e. an urgent, non-routine situation in which there are no alternatives for controlling the pest. Cotton growers were faced with a situation where they would expect significant economic loss without the use of sulfoxaflor to control the tarnished plant bug. No reported incidents were received by the Agency. This example demonstrates the strong benefits from the use that sulfoxaflor provides in critical pest situations.

During the public comment period for the proposed decision on the sulfoxaflor registration, comments were submitted by a variety of individual growers and grower organizations. They cited a number of situations in which sulfoxaflor registrations will replace older chemistries, including organophosphates and carbamates as well as pyrethroids and neonicotinoids. Commenters also indicated that for some use patterns, fewer applications of sulfoxalfor will be needed compared to other insecticides, which is especially protective of workers and also results in less environmental loading.

Individual growers and grower organizations also reported that sulfoxaflor will become an important pest management tool. It will be incorporated into Integrated Pest Management programs and is expected to have a role in controlling pests that had previously been extremely difficult to control. Citrus growers anticipate sulfoxaflor will be critical in their struggle against the Asian citrus psyllid, the vector of Huanglongbing disease, an invasive bacterium that is devastating to the citrus industry. In addition, the apple growers are anxious for the use of sulfoxaflor to control the woolly apple aphid. These comments all suggest that sulfoxaflor use will bring some benefits to the marketplace when compared to the alternatives.

While there is potential hazard to bees from exposure, EPA believes that the hazard will be appropriately mitigated by the protective statements that limit applications to when bees are not expected to be present. EPA has concluded that sulfoxaflor applied according to the label will not present unreasonable adverse effects against bees, and that the benefits of the compound compared to the registered alternatives, as well as its ability to control problematic target pests, justify registration.

B. Data Requirements

The database for sulfoxaflor is complete. No additional data is required.

C. Sulfoxaflor Label Mitigation

The Agency is requiring application restrictions designed to minimize exposure and protect non-target organisms. With the inclusion of reduced application rates, increased minimum application

intervals, and the pollinator-related labeling mitigation noted below, the remaining eco-risks are outweighed by the benefits of sulfoxaflor registration.

As sulfoxaflor is an insecticide, it may present potential risk to bees. Therefore the Agency required application restrictions designed to protect bees. The approved labels contain the following mitigation measures:

Crops that are not overly attractive to bees	**Pests**	**Mitigation**
Bulb vegetables	Onion thrips	Added "Do not apply this product at any time between 3 days prior to bloom and until after petal fall" for grains, bulb vegetables, leafy vegetables, root and tuber vegetables (except potato), turfgrass, and watercress. Reduced max single application rate from 0.9 lbs ai/A to 0.69 lbs ai/A for potatoes. Increased the minimum treatment interval from 7 to 14 days for potatoes. Reduced application rate from 0.133 lbs ai/A to 0.09 lbs ai/A for turfgrass.
Grains	Aphids	
Leafy vegetables	Aphids, silver whitefly, sweet potato whitefly, thrips	
Root and tuber vegetables and leaves of root and tuber vegetables	Aphids, leafhoppers, Silverleaf whitefly, sweet potato whitefly	
Turfgrass (grown for seed)	Aphids, chinch bugs	
Watercress	Aphids, silver whitefly, sweet potato whitefly, thrips	
Crops that are mildly attractive to bees	**Pests**	**Mitigation**
Brassica leafy vegetables	Aphids, silverleaf whitefly, sweet potato whitefly, thrips	Added , "Do not apply this product at any time between 3 days prior to bloom and until after petal fall" for *Brassica* leafy vegetables, pistachio and tree nuts. Reduced max single application rate from 0.133 lbs ai/A to 0.09 lbs ai/A for pistachio and tree nuts. Reduced max. single application rate from 0.9 lbs ai/A to 0.69 lbs ai/A for okra, soybeans, and succulent/dry beans. Increased the minimum treatment interval from 7 to 14 days for soybeans and Succulent/dry beans.
Okra	Aphids, plant bugs, greenhouse whitefly, silverleaf whitefly, sweet potato whitefly, thrips	
Pistachio and tree nuts	Aphids, San Jose	

	scale	
Soybeans	Soybean aphid, brown stink bug, southern green stink bug	
Succulent/dry beans	Aphids, plant bugs, brown stink bug, southern green stink bug, thrips	
Crops that are mildly to highly attractive to bees	**Pests**	**Mitigation**
Ornamentals	Aphids, mealybugs, scales, whiteflies	Reduced max single application rate from 0.133 lbs ai/A to 0.09 lbs ai/A for stone fruit. Increased the minimum treatment interval from 7 to 14 days for ornamentals. For ornamentals, allowed only one application during bloom, and restricted the single application during bloom to no more than 0.07 lbs ai/A. For ornamentals and strawberries, added: "Advisory Pollinator Statement: Notifying known beekeepers within 1 mile of the treatment area 48 hours before the product is applied will allow them to take additional steps to protect their bees. Also, limiting application to times when managed bees and native pollinators are least active, e.g., before 7 am or after 7 pm local time or when the temperature is below 55° F at the site of application, will minimize risk to bees." Added, "Do not apply this product at any time between 3 days prior to bloom and until after petal fall" for small berries (except strawberries) and stone fruit.
Small berries (except strawberries)	Grape leafhopper, mealybugs, plant bugs, thrips	
Stone fruit	Aphids, San Jose scale, weatern flower thrips	
Crops that are highly attractive to bees	**Pests**	**Mitigation**
Canola	Aphids	Reduced max single application rate from 0.133 lbs ai/A to 0.09 lbs ai/A for pome fruit. Added "Do not apply this product at any time between 3 days prior to bloom and until after petal fall" for canola and pome fruit.
Pome fruit	Aphids, plant bugs, white apple leafhopper, pear psylla, San Jose scale	

Crops that continually flower	Pests	Mitigation
Cotton (low to moderately attractive to bees)	Cotton aphid, cotton fleahopper, tarnished plant bug, western tarnished plant bug, Silverleaf whitefly, sweet potato whitefly, thrips, brown stink bug, southern green stink bug	Reduced max. single application rate from 0.9 lbs ai/A to 0.069 lbs ai/A for cotton, cucurbits, fruiting vegetables, and strawberry. Reduced max single application rate from 0.133 lbs ai/A to 0.09 lbs ai/A for citrus and allowed only one application during bloom. Increased the minimum treatment interval from 7 to 14 days for citrus. For cucurbits, strawberries and citrus, added: "Advisory Pollinator Statement: Notifying known beekeepers within 1 mile of the treatment area 48 hours before the product is applied will allow them to take additional steps to protect their bees. Also, limiting application to times when managed bees and native pollinators are least active, e.g., before 7 am or after 7 pm local time or when the temperature is below 55° F at the site of application, will minimize risk to bees." For cotton: Added advisory BMP language to notify known beekeepers 48 hour prior to application.
Cucurbits (highly attractive to bees)	Aphids, Silverleaf whitefly, sweet potato whitefly, thrips	
Fruiting vegetables (not overly attractive to bees)	Aphids, plant bugs, greenhouse whitefly, Silverleaf whitefly, sweet potato whitefly, thrips	
Strawberry (moderately to highly attractive to bees)	Plant bugs, thrips	
Citrus (highly attractive to bees)	Asian citrus psyllid, aphids, citrus snow scale, mealybugs, citrus thrips, florida red scale, California red scale, citricola scale	

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Sulfoxaflor: Response to Public Comments on EPA's "Proposed Registration of the New Active Ingredient Sulfoxaflor for Use on Multiple Commodities, Turfgrass, and Ornamentals" (Docket # EPA-HQ-OPP-2010-0889)

1) Conditional registrations

Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384): Once again EPA is proposing to repeat missteps of the past by registering a pesticide known to be toxic to non-target organisms without all required data to ensure its safety. As already seen with the neonicotinoid, clothianidin, and the herbicide aminocyclopyrachlor (Imprelis®), conditional registration without relevant ecological data can be detrimental to non-target species. It was pointed out to the agency in previous communications, risks to honey bees far outweigh any economic, social or environmental benefit of conditional registration, given that the honey bee has a $15 billion impact on the agriculture sector and that millions of dollars are at stake for commercial beekeepers, not to mention the economic and environmental costs to native, wild pollinators.

Like clothianidin, we believe any conditional registration of sulfoxaflor is a violation of the terms set out in Section 3(c)(7)(A) [sic], in that registration will pose "unreasonable adverse effects on the environment." The *Federal Insecticide Fungicide and Rodenticide Act* (FIFRA) defines the term "unreasonable adverse effects on the environment" as ''(1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide…." EPA has determined that estimated sulfoxaflor residues in pollen and nectar will exceed levels of concern (LOC) for acute risks, but the effects on honey bee colonies are not yet fully understood. Initial tests on brood development were inconclusive. Information on residues and colony health are still outstanding. Given the high uncertainties that remain and initial results that point to high acute hazards, sulfoxaflor presents "unreasonable adverse effects" to bee species, and does not meet statutory standards for registration.

EPA has a long history of registering pesticides without adequately understanding and underestimating human and environmental health impacts. We urge EPA to take a more precautionary approach.

National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369): FIFRA requires a comprehensive set of studies on each pesticide prior to registration. For a Conditional registration, Section 3(7)(c) [sic] of the law states:

> *A conditional registration under this subparagraph shall be granted only if the Administrator determines that use of the pesticide during such period will not cause any*

unreasonable adverse effect on the environment, and that use of the pesticide is in the public interest.

The information in the docket is not sufficient for the Administrator to draw a definitive conclusion that there will be no unreasonable adverse effects. To the contrary, information EPA does already have suggests that sulfoxaflor is likely to be highly problematic for bees.

EPA's response:

Section 3(c)(7) of FIFRA provides EPA the authority to grant a "conditional registration" for a pesticide product under certain circumstances. The conditions on registrants under this authority involve a requirement to submit particular types of data by a specified date after the registration. In 1978 Congress gave EPA discretionary authority in section 3(c)(7)(C) of FIFRA to approve the registration of a product containing a new active ingredient for which EPA requires additional data, when doing so appeared both to meet the safety standard and to be in the public interest.

Where an application for a new active ingredient lacks some of the necessary data for which there has not been sufficient time to generate and submit since the imposition of the data requirement, EPA may grant a conditional registration under FIFRA 3(c)(7)(C) if EPA determines that 1) during the time needed to generate the necessary data, the pesticide will not cause unreasonable adverse effects on the environment; and 2) use of the pesticide is in the public interest.

EPA proposed on January 14, 2013 to grant a conditional registration under FIFRA 3(c)(7)(C), intending to require data to resolve any residual uncertainty on the potential effects of sulfoxaflor on brood development and long-term colony health at the maximum application rate originally proposed by the registrant and to determine whether this rate can be allowed in the future. After review of the public comments and further consideration of the database, EPA has concluded that an unconditional registration of sulfoxaflor, with lowered application rates and other mitigation is supported by the available data and therefore the appropriate regulatory decision.

EPA disagrees with the assertion that there is inadequate understanding of sulfoxaflor and that the human and environmental health impacts are underestimated. EPA conducted an extensive analysis of sulfoxaflor in collaboration with counterpart agencies in Canada and Australia. Scientists from all three authorities reviewed over 400 studies, peer reviewed the primary evaluations conducted by their international colleagues, and communicated extensively on specific disciplines and issues. Additional EPA committees further reviewed the work done under the joint review project.

Upon completion of the partnered international evaluation of the data, EPA specifically addressed risks to bees in the environmental fate and ecological risk assessment. EPA clearly documented the properties of sulfoxaflor that render it a potential concern to bees: high acute oral toxicity, foliar spray application on pollinator attractive crops, and systemic uptake in plants. Accordingly, EPA conducted a Tier 1 ecological risk assessment to characterize the potential risk concerns. As indicted in the response to comment category #5 below, EPA's Tier 1 ecological risk assessment indicated exceedence of the acute risk level of concern (RQ > 0.4) in only 4 of the 100+ residue samples taken for sulfoxaflor in nectar (the dominant route of oral exposure for foraging bees). Two of these samples were from the highest proposed application rate (0.134 lb a.i./A), which has subsequently been reduced to a maximum of 0.086 lb a.i./A. At 0.086 lb a.i./A and below, only two of the 100+ residue samples have detectable levels of sulfoxaflor that exceed the LOC of 0.4.

Of the six colony-level (Tier 2) toxicity studies available for sulfoxaflor, EPA notes that none of these studies demonstrated a substantial treatment-related decline in colony strength (a key indicator of overall

colony health) following confined exposure of bees to sulfoxaflor foliar spray applications. EPA further notes that due to uncertainties associated with the application rates used in these studies and the aforementioned results from the Tier 1 risk assessment, EPA proposed reducing the maximum application rate of sulfoxaflor from 0.134 lb a.i./A to 0.086 lb a.i./A. This lower maximum application rate was evaluated in two of the available semi-field studies. Notably, the cotton tunnel study, which includes the maximum seasonal rate of 0.266 lb a.i./A, indicated that colony strength was similar across all treatments relative to pre-application conditions of the hives.

Consistent with the conclusions of the joint review project and EPA's risk assessment, the Pesticide Registration and Control Division of the Department of Agriculture, Food & the Marine in Kildare, Ireland, serving as the rapporteur member state for the European Union, reported on their summary, evaluation and assessment of sulfoxaflor. Regarding potential risks to bees, they stated that no unacceptable acute or chronic effects on colony survival and development were noted. They concluded that the risk to bees from the proposed uses of sulfoxaflor and its formulated products is acceptable.

2) Resistance concerns and alternative pesticides

Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384): While surveys have shown neonicotinoid resistance to still be restricted to very few species and often very localized in extent,[1] it is predictable that the widespread use of neonicotinoid insecticides will continue to give way to increased insect resistance. There is reported imidacloprid resistance in certain aphid species, with cross-resistance to other neonicotinoids.[2] One study documented acetamiprid, clothianidin and thiamethoxam resistance at 6.4, 10, and 22-fold, respectively in cotton aphids (*Aphis gossypii).*[3] High levels of cross-resistance to thiamethoxam, imidacloprid, and acetamiprid have also been detected in silver whitefly (*B. tabaci*).[4] Insects with neonicotinoid resistance have also been shown to have varying resistance to organophosphates, carbamates, and pyrethroids.[5] Due to growing resistance among insect populations, stronger pesticides with novel mode of actions are being sought. In the case of sulfoxaflor, it is stable in the presence monooxogenase enzymes –responsible for metabolizing chemicals and known to be involved in resistance to the neonicotinoids and other insecticides[6]- making sulfoxaflor a more potent insecticide to the insect. Industry is advertising sulfoxaflor as a "critical tool for insect resistance management," due to its new mode of action and its effectiveness on insect populations resistant to neonicotinoid and other insecticides.[7]

According to some industry scientists, sulfoxaflor has a pharmacological profile (in aphids) consistent with that of imidacloprid, suggesting that sulfoxaflor be considered a neonicotinoid.[8] However, others

[1] Nauen, R and Denholm, I. 2005. Resistance of Insect Pests to Neonicotinoid Insecticides: Current Status and Future Prospects. Archives of Insect Biochemistry and Physiology 58:200–215

[2] Nauen R, Vontas J, Kaussmann M, Wölfel K. 2012. Pymetrozine is hydroxylated by CYP6CM1, a cytochrome P450 conferring neonicotinoid resistance in Bemisia tabaci. *Pest Manag Sci*. 2 doi: 10.1002/ps.3460

[3] Herron, G. A. and Wilson, L. J. 2011. Neonicotinoid resistance in *Aphis gossypii* Glover (Aphididae: Hemiptera) from Australian cotton. Australian Journal of Entomology, 50: 93–98.

[4] Nauen, R and Denholm, I. 2005. Resistance of Insect Pests to Neonicotinoid Insecticides: Current Status and Future Prospects. Archives of Insect Biochemistry and Physiology 58:200–215

[5] Nauen, R and Denholm, I. 2005. Resistance of Insect Pests to Neonicotinoid Insecticides: Current Status and Future Prospects. Archives of Insect Biochemistry and Physiology 58:200–215.

[6] Sparks, T, DeBoer, G, et al. 2012. Differential metabolism of sulfoximine and neonicotinoid insecticides by *Drosophila melanogaster* monooxygenase CYP6G1. Pest Biochem. Phys. 103 (2012) 159–165

[7] Annetts, R and Elias, N. 2012. Sulfoxaflor For Management Of Cotton Pests In Australia. Presented at the *Australian Cotton Conference,* Management of Cotton Aphids. Available at http://www.australiancottonconference.com.au/2012-presentations-papers/annetts-robert

[8] Cutler P, Slater R, Edmunds AJ et al. 2012. Investigating the mode of action of sulfoxaflor: a fourth-generation neonicotinoid. *Pest Manag Sci.*

at Dow AgroSciences laboratories argue that the very high efficacy at nAChRs, coupled with its chemical structure, lack of cross-resistance, and metabolic stability,[9] prove that sulfoxaflor is a novel insecticide. Sulfoxaflor has been demonstrated to exhibit very low resistance in some aphid species (e.g. silverleaf and greenhouse whiteflies) already resistant to imidacloprid with no evidence of cross resistance to other neonicotinoid pesticides, making it a good candidate to control pests already resistant to certain neonicotinoids.[10] [11] One study investigating the efficacy of sulfoxaflor in the field, determined that sulfoxaflor proved to be more "residual and significantly more potent," even with similar speed of action when compared to neonicotinoids.[12]

The evolution of insect resistance is predictable, leading to farmers resorting to multiple chemicals, alternating insecticides with different modes of action (which would have to be either more toxic, or used in greater frequency), in order to control resistant insects. However, the risks to non-target insects in the advent of failed technologies are not seriously considered.

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): Sulfoxaflor should be considered a subcategory of the neonicotinoid class of insecticides rather than the first member of the sulfoximine insecticide class based on its similarities in mode of action and its structure that mimics the neonicotinoid toxicophore. This classification should be taken into account for insecticide resistance management plans.[13] While the applicant, Dow AgroSciences, has asserted in published literature that sulfoxaflor is the first insecticide in the new sulfoximine class of chemicals[14] (distinct from the neonicotinoids), other assessments of the compound suggest that it may instead be a new subclass of the neonicotinoids.[15] EPA refers to sulfoxaflor as "the only member of the sulfoxamine subclass of neonicotinoid insecticides" in the beginning of its RA, but later mentions that it is distinct from the neonicotinoids for insecticide resistance management.[16] EPA should resolve this confusion and clarify that sulfoxaflor is a subclass of neonicotinoids in light of the conflicting information from the applicant and the agency.

An investigation of sulfoxaflor's mode of action found that it interacts with the high-affinity imidacloprid binding site in the insect's nAChR.[17] Sulfoxaflor also behaves in a method similar to imidacloprid *in situ* in aphids at both the receptor and neuronal levels.[18] These characteristics could pose problems for cross-resistance with neonicotinoids, and should be factored into insecticide resistance management plans. Most of the currently-identified resistance to commercialized neonicotinoids is caused by enhanced monooxygenase metabolism.[19] Sulfoxaflor is stable to monooxygenases, so it can control pests that have developed metabolic resistance to the neonicotinoids.[20] However, resistance can also be conferred by a target site mutation that sulfoxaflor

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doi: 10.1002/ps.3413.

[9] Watson GB, Loso MR, Babcock JM, et al. 2011. Novel nicotinic action of the sulfoximine insecticide sulfoxaflor. *Insect Biochem Mol Biol.* (7):432-9.

[10] Longhurst C, Babcock JM, Denholm I, Gorman K, Thomas JD, Sparks TC. 2012. Cross-resistance relationships of the sulfoximine insecticide sulfoxaflor with neonicotinoids and other insecticides in the whiteflies Bemisia tabaci and Trialeurodes vaporariorum. *Pest Manag Sci*. doi: 10.1002/ps.3439.

[11] Siebert, M, et al.2012. Field Evaluations of Sulfoxaflor, a Novel Insecticide, Against Tarnished Plant Bug (Hemiptera: Miridae) in Cotton . *J Cotton Science 16:129–143*

[12] Lysandrou, M, Ahmad, M and Longhurst, C. 2010. Comparative Efficacy Of Sulfoxaflor Against Cotton Leafhopper, *Amrasca Devastans* (Distant) (Cicadellidae: Homoptera) Under Field Conditions Of Punjab And Sindh. *J. Agric. Res*.48(4)

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[14] Babcock JM, et al. 2010. Biological characterization of sulfoxaflor, a novel insecticide. *Pest Manag Sci*. 67(3): 328-334.

[15] Cutler P, et al. 2012.

[16] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 8.

[17] Cutler P, et al. 2012.

[18] Cutler P, et al. 2012.

[19] Babcock JM, et al. 2010.

[20] Cutler P, et al. 2012.

was susceptible to in trials, a type of resistance that is not discussed in the RA's discussion of cross-resistance.[21] [22] The levels of resistance to sulfoxaflor identified in strains with target-site mutations could have a major impact on field performance of these products.[23] Sulfoxaflor's mode of action is not yet fully understood, and initial results show some cross-resistance with neonicotinoids, which should lead to their categorization as neonicotinoids to manage insecticide resistance. The concerns about potential cross-resistance with commercial neonicotinoids should be further explored, and are not addressed adequately in the evaluation of sulfoxaflor's proposed registration.

David Kerns' (LSU AgCenter) comment (Docket # EPA-HQ-OPP-2010-0889-0059): Based on my evaluations, sulfoxaflor appears to have an excellent fit in the Mid-South's cotton production system; having excellent efficacy towards tarnished plant bug, cotton fleahopper and cotton aphid. Additionally, the use of sulfoxaflor as an alternative to a number of insecticides currently used for plant bug management should help alleviate problems associated with destruction of natural enemies, pest resurgence and secondary pest outbreaks.

The Mid-South cotton producing states including Tennessee, Arkansas, Mississippi and Louisiana have had extremely difficult problems effectively controlling tarnished plant bug in cotton, and subsequent secondary pest outbreaks. Tarnished plant bugs are a key pest of cotton and have been the number one yield limiting pest for more than 10 years. Plant bugs damage cotton primarily by feeding on the squares (flower buds) causing them to abort. Thus the fruit is lost resulting in a reduction in lint. Tarnished plant bugs are usually most abundant once the cotton crop begins to flower, and they will remain potential pests until all of the harvestable fruit are set. Thus it is imperative that cotton be protected from excessive plant bug injury from square formation until crop cutout.

Growers utilize a number of integrated approaches for managing plant bugs in cotton including: planting more tolerant varieties, landscape manipulated to avoid placement of cotton adjacent to corn, managing weeds that host plant bugs, and utilizing insecticides. The insecticides used for managing plant bugs in cotton rely heavily on organophosphates and neonicotinoids. Due to resistance issues we have seen a shift to acephate synergized with pyrethroids, and neonicotinoid/pyrethroid mixtures. These mixtures have been effective but short lived; when immigrating plant bug populations are high, it is not uncommon to have to retreat fields within 5 days. Cotton growing in areas with naturally high plant bug populations in the landscape may require as many as 10 insecticide applications during a year.

Unfortunately these insecticides have detrimental effects on arthropod natural enemies leading to outbreaks of secondary pests. Acephate is notorious for flaring spider mites, and pyrethroids are notorious for flaring spider mites and aphids. Thus, follow up applications of miticides or aphicides are often necessary following insecticide applications targeting plant bugs. Some of the neonicotinoids have proved efficacious towards aphids, but in recent years resistance to most of these products has been widespread. Additionally, the neonicotinoids were once thought to have marginal impact on arthropod natural enemies, but in research I have conducted over the past 4 years, I have found these products to be extremely harmful towards lady beetle larvae. Therefore, not only are we seeing aphids develop resistance to some neonicotinoids, but these same products are destroying the aphid's natural enemies. Sulfoxaflor however, is one of the best aphicides I have evaluated, and thus

[21] Cutler P, et al. 2012.
[22] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 14.
[23] Cutler P, et al. 2012.

flaring aphids would not be likely. Additionally, I was suspicious that sulfoxaflor, because it has a similar mode of action to the neonicotinoids, might also be harsh on lady beetle larvae, but this has not been the case. My data suggests it is much softer than any of the neonicotinoids I have tested. In many respects sulfoxaflor appears to be very different from the neonicotinoids, not only in its lesser impact on arthropod natural enemies, but research has demonstrated that aphids resistant to neonicotinoids are not cross resistant to sulfoxaflor.

Without access to new and improved insecticide chemistries to manage our insect pests we will only see increased reliance and use of the older, harsh insecticide chemistries; and continuation of the insecticide treadmill. Sulfoxaflor could replace a number of harsh insecticide applications with a product that is highly effective towards the target pests, safer towards a number of the key natural enemies, and much less likely to cause secondary pest outbreaks. These characteristics would make sulfoxaflor an excellent candidate for managing pests in Mid-South cotton, and ultimately becoming a cornerstone of a much more robust and effective cotton IPM program.

Elizabeth Beers' (WSU) comment (Docket # EPA-HQ-OPP-2010-0889-0266): As an industry, we have been relying solely on the neonicotinoid insecticides (IRAC Group 4A) for aphid control for nearly two decades. The extension of their spectrum into our key lepidopteran pests has increased the overall numbers of applications per season, without any rotational materials to fit into a resistance management plan. New modes of action are needed for these pests. In addition, the neonicotinoids are weak against one of more troublesome aphid species, woolly apple aphid. Unlike other aphid species, this pest causes chronic debilitation of the tree, and fruit contamination is cited frequently as a cause for rejection or fumigation of exported fruit. The last two conventional materials that were effective (endosulfan and diazinon) are being phased out, leaving a serious gap in our programs; sulfoxaflor is one of the few materials I have tested in the last 10 years that can control woolly apple aphid. Materials such spirotetramat provide a prophylactic alternative, but do not allow as much flexibility in IPM programs. For these reasons, I am happy to support the registration of sulfoxaflor in the tree fruit market.

Scott Stewart's (University of Tennessee) comment (Docket # EPA-HQ-OPP-2010-0889-0266): Given well established and increasing resistance to alternative insecticides, sulfoxaflor has a real fit in managing infestations of tarnished plant bugs and cotton aphids. Sulfoxaflor represents a new mode of action that will replace applications of neonicotinoid, pyrethroid, and organophosphate insecticides. Many of my efficacy trials with sulfoxaflor are available on the internet at http://www.utcrops.com/MultiState/MultiState.htm (or upon request). My testing indicates that sulfoxaflor provides control of tarnished plant bugs and cotton aphids that is equal to and typically superior to alternative insecticide. Thus, I expect sulfoxaflor to reduce the total number of foliar application needed to control insect pests in cotton.

Growers in the Midsouth have a critical need for new modes of action that control resistant insects and maintain profitability by providing better crop protection with fewer insecticide applications. Compared with many alternative insecticide options, the data suggests that sulfoxaflor is relatively "soft" on beneficial insect populations in cotton, and this may prevent additional applications targeting secondary pests such as spider mites and cotton aphids. Of course, the effects of insecticides on pollinators have been front and center during the last year. It has been suggested that the use of sulfoxaflor use be to the pre-flowering window in cotton to limit exposure to pollinators. This would greatly limit the potential benefits of this insecticide. The greatest need for plant bug control occurs during the blooming window, and frankly, I know of no reason to believe sulfoxaflor has any greater effect on pollinators than alternative insecticides. Indeed, I suspect the opposite, particularly given the rigorous scientific scrutiny applied during the registration process.

Tennessee utilized a limited amount of sulfoxaflor in 2012 under a Section 18. Growers and consultants were impressed with its performance in controlling tarnished plant bugs and protecting yield. I received no reports of performance failures, secondary pest outbreaks, bee kills or other negative effects. The data available indicates that sulfoxaflor is a relatively benign insecticide that represents a substantial improvement over alternative insecticides. I think the registration of sulfoxaflor will represent a step forward for both cotton producers and for "environmental health".

Roy Parker's (Texas A&M) comment (Docket # EPA-HQ-OPP-2010-0889-0210): Sulfoxaflor (Transform) has been included in my field studies on cotton during each of the past three years primarily for the control of cotton fleahopper and cotton aphid. In those studies I found it to be very effective in keeping the fleahopper below economic injury level with performance equal to the neonicotinoids and organophosphates. In addition, the chemistry provided outstanding control of the cotton aphid. The combination of effective fleahopper and aphid control provides an advantage in that treatment for the fleahopper does not result in resurgence of cotton aphis. Therefore, it has a good fit in an integrated pest management program by reducing the needed to apply an additional treatment for cotton aphid at a later date. Although some of the neonicotinoids also provide similar aphis control (recuded potential for aphis increase), the availability of the different mode of action provided by sulfoxaflor allows us to use different chemistry in cotton where neonicotinoids are being used extensively. We need this different mode of action available as an insecticide resistance management tool.

My studies demonstrate that one to three treatments for the cotton fleahopper are required from initiation of squaring (bud formation) through the first week of bloom. In some years, depending upon growing conditions, cotton lint yields are greatly enhanced by control of the cotton fleahopper.

Western Growers' comment (Docket # EPA-HQ-OPP-2010-0889-0362): Some of the products our industry has relied on for years to control aphids have either been phased out or restrictions have been added to labels making them more difficult to use. The registration of new, effective aphid control products is critical for continued production of these crops. Research data from University of California and University of Arizona demonstrate that Closer Insecticide provides excellent control of all aphid species damaging cole crops and leafy vegetables. Closer is used at a very low use rate. The proposed use parameters such as the pre harvest interval and restricted entry interval for this product are very compatible with the production systems used by our grower members.

Another key pest in leafy vegetables, cole crops as well as melons and fruiting vegetables is whitefly. Whitefly feeding produces honeydew which can make harvest difficult and reduce quality. Whitefly also transmits plant viruses which can dramatically reduce crop yield and quality. Effective control of whiteflies is a must for producing high quality crops, especially in desert production areas where whitefly populations can be very damaging. Whiteflies have demonstrated an ability to develop resistance to insecticides very quickly so it is important to have multiple modes of action available. Research data from University of Arizona has shown that Closer is effective in controlling whitefly and has been demonstrated to reduce virus incidence in fall melons.

Due to restrictions and removal of some key insecticides in strawberries such as Lannate (methomyl), insect pest management has become more challenging. One of the most serious pests is Lygus. This insect can cause great losses for strawberry growers from feeding on developing flowers resulting in malformed fruit which is unmarketable. Left untreated, losses of greater than 50% of the crop are

possible. Research trials conducted in 2012 by the CA Strawberry Commission in conjunction with University of California demonstrated significant increases in marketable yields. Closer will be a critical tool for growers in controlling this challenging pest.

We understand that some crops have language restricting use during and around bloom. In crops like melons and strawberries bloom occurs early and throughout a large part of the life cycle of the plant. Therefore, it is critical to have flexible application restrictions to be able to effectively use this and other products. The insect control spectrum of Closer paired with its unique mode of action make it an important new tool for our growers.

Anonymous extension entomologist's (MSU) comment (Docket # EPA-HQ-OPP-2010-0889-0062): I am an Extension Entomologist at Mississippi State University with statewide responsibilities in cotton, corn, soybean, wheat, and grain sorghum. I have tested Sulfoxaflor extensively over the last several years in cotton against tarnished plant bugs and cotton aphids. Tarnished plant bugs are the number one insect pest of cotton in Mississippi often requiring 8-12 applications for this pest alone in the Delta region of the state. This is due to widespread resistance to other classes of chemistry. Sulfoxaflor offers producers a new mode of action to rotate into their management program that will replace neonicotinoid applications prior to bloom and organophosphate applications after bloom with increased efficacy over existing products which possibly may further eliminate follow up applications with less efficacious products. Also, because this product is equally effective on cotton aphids, it will save one application of a neonicotinoid when both pests are present at the same time since Mississippi no longer has effective insecticides that control tarnished plant bugs and cotton aphids at the same time.

It is critical to producers in Mississippi and the Mid-Southern area that they have access to new modes of action to control resistant insects such as tarnished plant bugs and cotton aphids season long. It needs to be further emphasized that use of this product will not add additional applications but rather replace older more harsh chemistry. I have seen the beneficial insect profile from entomologist at other universities and it has much less impact on the beneficial insects present in cotton which again may further reduce total insecticide usage. Furthermore, I realize that there is some concern with bee keepers anytime a new insecticide is released. However, any new insecticide that is released today undergoes much more scrutiny and testing as new scientific testing procedures are developed and incorporated into the registrant's application process. Again, because this is a new compound that has proven to be a "softer" chemistry on beneficial insects and bees it will replace applications of older chemistry that is much more disruptive to the system. This should be viewed as positive benefit to the whole industry.

Larry Godfrey's (UC Davis) comment summary (Docket # EPA-HQ-OPP-2010-0889-0278): Sulfoxaflor, based on my research, appears to be uniquely situated to contribute positively to integrated pest management programs of cotton in California. The pest spectrum of sulfoxaflor, western tarnished plant bugs (Lygus hesperus) and cotton aphids (Aphis gossypii), represent two of the most damaging and economically-concerning pests of cotton. Based on annual estimates of cotton crop losses made by cotton entomologists in California (as well as in other states), L. hesperus generally causes the greatest yield loss among arthropod pests of cotton in California. Depending on the year, up to a 5% loss is recorded in spite of the use of recommended management practices. This pest infests numerous crops in the San Joaquin Valley (SJV) and flourishes in the intensive agriculture of this production area. IPM specialists have developed a well-balanced program for managing L. hesperus in cotton utilizing cultural controls, biological controls, a vigorously-growing/well-managed cotton crop, but insecticides are still needed to prevent economic losses in the cotton crop. The dynamic nature of this pest and intricacies of this production system mean that non-chemical methods alone are not sufficient. During my 20-year career, cotton growers have relied on

carbamate, organophosphate, and pyrethroid insecticides for lygus management. The former two classes of chemistry have largely been removed from the "toolbox" due to insecticide resistance in L. hesperus and regulatory actions with the loss of aldicarb (Temik®) being the most recent action. Pyrethroid insecticides have been used for the last ~15 years and were the standard insecticide treatment for lygus in the SJV. This class of chemistry "stressed" the IPM programs due to their broad-spectrum nature and propensity to kill natural enemies which promoted populations of cotton aphids (therefore creating a secondary pest and additional insecticide applications). Insecticide resistance is presently developing to lygus bugs in the San Joaquin Valley to pyrethroid insecticides and growers are in need of alternative insecticidal approaches. Flonicamid was registered ~5 years ago and is presently very effective against lygus bugs in cotton and heavily used by cotton growers. Resistance to this active ingredient has not yet been detected but having insecticide rotational partners such as sulfoxaflor is the optimal scenario in order to provide sustainable IPM programs, i.e., protect all available effective chemistry from the development of resistance.

A. gossypii, the other primary target of sulfoxaflor in the SJV, while also potentially reducing lint yield, has the most potential to negatively impact cotton lint quality. During the period of open lint, feeding by aphids potentially results in honeydew deposition on the lint which reduces the quality and ability to process the lint. In the worst case scenario, a production region gains the reputation of producing "sticky cotton" and long-term ramifications on marketability of the cotton can result. Presently in the SJV, cotton aphid management relies on applications of chlorpyrifos and neonicotinoid insecticides. During the late-season period (August to harvest), my research has shown the aphid threshold for sticky cotton is very low (5 to 10 aphids per leaf), so growers pay close attention to management of this pest. Both of these insecticides are under scrutiny with chlorpyrifos use being examined due to water quality issues. In addition, aphid resistance to the neonicotinoid insecticides is widespread in Mid-South cotton and, given 15 years of use in the SJV, is likely to occur or perhaps already present at some level. Flonicamid is also highly effective against cotton aphids but this insecticide is generally "reserved" for use against lygus bugs (or has already been used during the season prior to the need for cotton aphids which generally infest ~4-6 weeks after lygus bugs).

Sulfoxaflor has less impact on populations of natural enemies than the other insecticides used for lygus bug management (pyrethroids) and protecting these beneficials helps to keep other arthropod pest populations in check (late-season spider mites, beet armyworms, whiteflies, etc.). This helps to reduce treatment needs for these pests. Finally, sulfoxaflor in my research has provided excellent protection of cotton yields which will promote the profitability of cotton and its role in the agricultural economy.

Beth Grafton-Cardwell's (UC Riverside) comment (Docket # EPA-HQ-OPP-2010-0889-0161): I have conducted a research and extension program for 23 years on the subject of integrated pest management of citrus pests in the San Joaquin Valley of California. U have worked with sulfoxaflor since 2009 and studied its impact on a key pest of citrus, the citricola scale, *Coccus pseudomagnoliarum*. Currently, citricola scale is controlled primarily with the organophosphate insecticide chlorpyrifos. Reliance on chlorpyrifos ot manage citricola scale has resulted in the development of resistant populations and new insecticides such as sulfoxaflor are needed as rotational chemistries to control the pest. A single application per year of sulfoxaflor in the rate range of 7.13 to 8.55 oz per acre which is 100-150 gm ai/acre is very effective in controlling citricola scale. Citricola scale often requires a higher concentration of insecticide than other insect pests, because the water volume that is applied to achieve coverage of the tree and ensure contract with the insect is 3—500 gallons per acre. Registration of sulfoxaflor at 8.55 oz/acre will reduce the number of applications of

chlorpyrifos used for this pest in the San Joaquin valley. Lower concentrations of sulfoxaflor are likely to require more frequent applications of this or other pesticides to control citricola scale.

Jeffrey Gore (Mississippi State Univ) comment (Docket ID No. EPA-HQ-OPP-2010-0889-0308): The purpose of this letter is to support the registration of sulfoxaflor, a new insecticidal active ingredient. I am an assistant professor at the Mississippi State University, Delta Research and Extension Center in Stoneville, MS. I am an Entomologist with responsibilities for insect control in row crops grown in Mississippi. Currently, producers in the midsouthern U.S. face numerous challenges in crop production. Weed and insect species that have developed resistance to numerous pesticides have created a unique challenge that threatens the economic viability of many growers. In relation to sulfoxaflor, cotton producers in Mississippi have two important insect pest species that are resistant to most of the insecticides currently labeled for their control. The tarnished plant bug, *Lygus lineolaris,* has become the most important insect pest of cotton in the Mid-South. Growers in my region of Mississippi generally make 5-12 applications annually targeting this insect. The development of resistance to pyrethroids, organophosphates, and carbamates in the tarnished plant bug is the most important cause for the increased numbers of applications targeting this insect. Currently, the neonicotinoid class of insecticides and the insect growth regulator, novaluron, are the only effective insecticides for which resistance has not been documented in tarnished plant bug. As a result, cotton growers in Mississippi have had to rely heavily on insecticides in the neonicotinoid class and the frequency of applications with neonicotinoids has increased in recent years. Coincidentally, the increased frequency of neonicotinoid applications targeting tarnished plant bug has inadvertently selected for cotton aphid population with high levels of resistance to this insecticide class. The only effective insecticide labeled for cotton aphid control is the pyridine carboxamide, flonicamid.

Another consequence of the increased applications needed to manage insecticide resistant tarnished plant bug is outbreaks of spider mites. Twospotted spider mite has become a season long pest of cotton in Mississippi. The increased incidence of acaricide applications targeting spider mites has coincided with the occurrence of insecticide resistance in tarnished plant bug and there is a strong correlation between the numbers of applications for spider mites and the numbers of applications for tarnished plant bug. Increased applications with high rates of broad spectrum insecticides such as pyrethroids, organophosphates, and neonicotinoids eliminate natural enemy complexes in cotton and create an ideal environment for outbreaks of spider mites. Research by a recent graduate student in Mississippi showed that foliar applications of neonicotinoids, pyrethroids, and organophosphates can flare spider mites in cotton. This has created an additional input cost for growers in the Delta regions of the Mid-South.
I have been testing sulfoxaflor for the last six years in cotton. My research has involved field experiments evaluating the control of both tarnished plant bug and cotton aphid with sulfoxaflor in cotton and comparing it to currently labeled insecticides. Sulfoxaflor has performed well in all of those experiments and is comparable to our current standards. In Mississippi, the current standard for control of tarnished plant bug is 1.0 lbs ai/A of acephate tank mixed with a pyrethroid or 0.05 lbs ai/A of thiamethoxam mixed with a pyrethroid. Sulfoxaflor applied at 0.047 lbs al/A alone has performed as good, or better than these treatments. Similarly, sulfoxaflor applied at 0.023 to 0.047 lbs ai/A has performed better than the currently labeled insecticides against cotton aphid.

The Delta counties of Mississippi were fortunate to be granted a Section 18 for the use of sulfoxaflor in 2012. I was able to view the performance of sulfoxaflor in large field situations and it performed similarly to what I previously observed in small plot replicated trials. Consultants and growers were generally happy with how sulfoxaflor performed on their fields in Mississippi.

In addition to good control of target pests with sulfoxaflor, there are minimal, if any, non-target effects with this insecticide. In research plots, we have not seen an increased incidence of twospotted spider mite following sulfoxaflor applications. Also, because sulfoxaflor has good activity against both tarnished plant bug and cotton aphid, it will be the only insecticide that will effectively control both species in cotton. Because of these factors, sulfoxaflor is an important insecticide for the future sustainability of cotton production in many areas of the Mid-South. Sulfoxaflor will likely replace 1-2 applications of neonicotinoids during the early season and 1-2 applications of organophosphate/pyrethroid tank mixtures later in the season. Also, because it his little non-target effect and controls cotton aphids, the numbers of applications targeting other arthropod pests may also be reduced. Finally, the selective nature of sulfoxaflor, high level of control against target pests, and low use rates will provide a valuable tool for cotton growers in Mississippi. Sulfoxaflor will allow us to design a more effective insecticide rotation strategy that will minimize the economic impacts of multiple pest species and reduce the selection pressure on other classes of insecticides.

EPA's response:

During the public comment period for this proposed registration decision, EPA received comments supporting the Agency's determination that the benefits of sulfoxaflor outweigh the risks. These comments were from organizations representing numerous growers of a wide variety of crops, including minor use crops. The groups included the California League of Food Processors (0250), Washington State Potato Commission (0275), US Canola Association (0279), the American Soybean Association (0305), the National Sunflower Association (0307), the California Grape and Fruit Trade (0312), the California Specialty Crops Council (0313), the National Cotton Council (0317), the California Strawberry Commission and the United Fresh Product Association (0379). Individual growers also commented, as did a number of researchers who have long studied insecticide resistance management. These researchers not only have expertise in this area but indicated that their careers and livelihood are based on years of studying insecticide resistance management and have personal knowledge of product performance based on their experiences leading research in the field.

As stated by David Kerns (comment #059, above), cotton growers have developed various strategies for combating plant bugs but have had to rely heavily on organophosphates and neonicotinoids, with as many as 10 insecticide applications per year. As stated in his comment, these older chemistries can flare up other target pests resulting in even more pesticide applications. These additional applications would be expected to be harmful to pollinators.

Both Elizabeth Beers (comment #0266) and Roy Parker (comment #0210) believe that sulfoxaflor would be of benefit to growers in targeting pests that have developed resistance to neonicotinoids. Their comments regarding research in this area support the position that sulfoxaflor will fit into IPM programs. This is further supported by the comment from Mississippi State University (#0062) that sulfoxaflor's new mode of action will replace neonicotinoid and organophosphate applications as well as reduce the number of applications of insecticides to cotton.

These comments from researchers, who are actively engaged in pest management research, provide further evidence to EPA's conclusion that sulfoxaflor is different from the registered neonicotinoids. Not all chemicals in the Insecticide Resistance Action Committee (IRAC) Group 4 classification have comparable efficacy on target pests and/or comparable risk to non-target organisms. The primary site of action for Group 4 compounds is the nicotinic acetylcholine receptor. Subclass 4A are the neonicotinoids. Even between this subclass, there are differences. The nitroguanidine subclass is highly toxic to honey bees while the cyanoamidine subclass is relatively nontoxic to honey bees. Group 4C is

assigned to sulfoxaflor which presents a different mode of action to the target site and thus appears to be efficacious against some resistant pests. Further, according to commenters # 0059, 0266, 0062, 0278 and 0308, they have seen evidence that sulfoxaflor is softer on beneficial insects than other available pesticides.

The commenter #0363 noted that, while sulfoxaflor activity was not affected by enhanced monooxygenase metabolism, the most common resistance mechanism in insects, there are other resistance mechanisms that can affect the activity of sulfoxaflor. EPA acknowledges that other mechanisms of resistance exist and may affect field performance of sulfoxaflor in the future. Currently, however, these resistance mechanisms are rare in field populations of insect pests and are not responsible for the vast majority of current cases of resistance. Therefore, in the short term, EPA believes that sulfoxaflor's lack of cross resistance will be useful for resistance management purposes. In the longer term, EPA acknowledges that other mechanisms of resistance may impact the performance of sulfoxaflor in the field and may necessitate continued vigilance in resistance management efforts. The Agency does not evaluate compounds based on potential mutations of the target site and future resistance. However, the labels include language regarding Integrated Pest Management (IPM) and Insecticide Resistance Management (IRM), to prevent the potential development of resistance to sulfoxaflor.

3) Sulfoxaflor degradates

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): While sulfoxaflor may biodegrade rapidly in aerobic conditions, its soil degradates are mobile and "expected to be highly persistent in aerobic soil/aquatic systems."[24] [25] Sulfoxaflor and all of its degradates should be included in all of the risk assessment calculations. The major degradate (X11719474 [X-474]) has a different mode of action and is less toxic than sulfoxaflor, but is also systemic and could be absorbed from the soil by target crops, or successive crops in the same fields because of its long half-life.[26] This would be of greater concern and would need to be revisited if a soil-applied use was approved, but is still an issue with the proposed application methods. One of the minor degradates (X11519540 [X-540]) is more toxic than sulfoxaflor but it forms at low concentrations so was mostly excluded from the risk assessments. For aquatic organisms, the RA only evaluated sulfoxaflor and X-540. While EPA asserts that "available evidence indicates that the X-474 degradate does not share the same MOA as the parent and is much less toxic based on measures of effect relevant to ecological risk assessment," this dismissal still represents a significant release of a compound into the environment about which little is known.[27] EPA goes on to state that "X-474 is expected to dominate the exposure resulting from use of sulfoxaflor," suggesting that it is irresponsible to exclude X-474 from both the aquatic and terrestrial RA.[28] The current RA is inadequate to assess the potential risks from the stable X-474 in the aquatic environment. For terrestrial organisms, the RA evaluates parent sulfoxaflor only. Given the rapid biodegradation of sulfoxaflor, and its metabolism into degradates in plant tissue, this is inadequate to protect terrestrial species that may be exposed to residues. The combination of water solubility, persistence, and toxicity (especially to bees and other insect pollinators) is particularly concerning because compounds with these same characteristics have shown adverse effects to non-target species. Sulfoxaflor and its degradates' persistence in the environment is concerning because of the numerous detrimental impacts to non-target organisms that

[24] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.
[25] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 37.
[26] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 46.
[27] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 8.
[28] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.

have not been fully assessed.

EPA's response:

For sulfoxaflor and other pesticides, identifying residues of concern for ecological risk requires consideration of exposure *and* ecotoxicological effects. As explained on page 17 of the Environmental Fate and Effects Division's assessment, the degradate X-474 is expected to be a "major" degradate (i.e., > 10% formation relative to the parent) in the aquatic and terrestrial ecosystems. However, multiple lines of evidence indicate that the X-474 does not possess the same ecotoxicological concerns as parent sulfoxaflor.

One important line of evidence is available toxicity data which indicates X-474 is "practically non-toxic" to multiple taxa including fish (rainbow trout), aquatic invertebrates (water flea), terrestrial invertebrates (honey bee), birds (bobwhite quail) and mammals (rat).

In addition to the low hazard the X-474 degradate poses to non-target animals, available information indicates the X-474 degradate does not share the same mode of action as parent sulfoxaflor. Empirically, this is demonstrated by the lack of acute toxicity of the X-474 degradate to the honey bee (oral acute LD_{50} > 100 ug a.i./bee) as compared to parent sulfoxaflor (oral acute LD_{50} = 0.13 to 0.38 ug a.i/bee). The minor degradate X-061 is similarly not acutely toxic to honey bee (LD_{50} > 104 ug a.i./bee).

In addition to empirical information, QSAR modeling for X-474 based on ECOSAR v 1.00 confirms its lack of acute toxicity to fish and aquatic invertebrates with predicted acute LC_{50} values of 740 and 240 mg /L respectively, based on the amide ECOSAR chemical class. QSAR modeling also indicates the chronic toxicity of X-474 to fish and aquatic invertebrates is relatively low, with predicted chronic values of 4.4 and 3.1 mg/L, respectively using ECOSAR and the amide chemical class. Chronic estimated environmental concentrations (EECs) for total sulfoxaflor residues (including X-474) are more than 100X below these predicted chronic values, thus indicating a large margin of safety with respect to chronic risk of the X-474 degradate to aquatic animals. Predicted 96-h EC_{50} and long-term toxicity values for green algae using ECOSAR are 1.8 and 0.5 mg/L, respectively, which are an order of magnitude above EECs for sulfoxaflor and all its degradates combined.

Lastly, the Agency notes that in its aquatic ecological risk assessment, it initially conducted a screening assessment by including all degradates of interest for sulfoxaflor in the aquatic EECs (parent + X-474+X-540) for efficiency purposes. As indicated in the Agency's ecological risk assessment document, risk quotients (RQ) based on these degradates of interest were well below acute and chronic levels of concern for fish, freshwater invertebrates and aquatic plants. Therefore, inclusion of the X-474 degradate would not alter the risk conclusions for these taxa. For two taxonomic groups, marginal exceedences of the listed species acute risk LOC of 0.05 and chronic LOC of 1.0 were observed using all of the residues of interest. Further refinement was conducted by including only those degradates of toxicological concern (parent chemical and X-540) which indicated no acute or chronic risk LOC was exceeded. Excluding the X-474 degradate was considered appropriate because of the low hazard it poses, as described above.

Therefore, based on multiple lines of evidence, the Agency believes the X-474 degradate should not be included as part of the toxic residues of concern for assessing ecological risks with sulfoxaflor.

4) Section 18 Exemptions

Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384): The registrant first submitted sulfoxaflor for registration in 2010. Since then several section 18 exemptions have been granted for sulfoxaflor for use in Louisiana (Dec 17, 2012), Mississippi (June 1, 2012), and Tennessee (June 1, 2012) for cotton to control for tarnished plant bugs (*Lygus lineolaris*) due to resistance issues. While FIFRA's section 18 allows for pesticides undergoing registration consideration to be candidates for exemption, it is still highly irresponsible for EPA to allow unregistered, unevaluated chemicals into the environment without fully understanding and assessing risks. Time-limited tolerances for sulfoxaflor residues were not published until September 2012. At this time, EPA issued tolerances for various cotton products, the lowest of which was 0.2ppm - in or on cotton and undelinted seed.[29] Tolerances of 6.0ppm and 0.35ppm were issued for other cotton commodities. Given that honey bees do visit cotton, mostly for nectar, and the agency has since established that residues higher than 0.07 ppm will pose a risk to bees, the section 18 exemption and tolerances undoubtedly created environmental risks to honey bees that the agency did not take into account at that time. It is not apparent whether EPA conducted an ecological assessment for these Section 18 exemptions. This is clearly a regulatory failure that has plagued section 18 exemptions for many years.

Section 18 of FIFRA authorizes the agency to allow a new use of a registered pesticide or the use of a pesticide whose registration is pending (and making progress toward registration) for a limited time if the agency determines that an emergency condition exists. EPA must perform a multi-disciplinary evaluation of the request including an ecological and environmental risk assessment. The agency must deny an exemption request if the pesticide does not meet safety standards, or if emergency criteria are not met. Without strict adherence to Section 18 criteria, allowance of unregistered pesticide uses and unregistered pesticides risks an environmental and public health problem. Similar to conditional registration, allowing a pesticide like sulfoxaflor into the environmental with unknown ecological hazards is a recipe for disaster.

EPA's response:

Section 18 of FIFRA authorizes EPA to exempt State and Federal agencies from any provision of FIFRA, if EPA determines that emergency conditions exist which require an exemption. EPA can exercise this authority through the procedures in 40 CFR Part 166 to allow the emergency use of pesticides. Whether a section 18 was properly granted in the past is irrelevant to the determination of whether to grant a registration now. In 2012, EPA granted emergency exemption use under section 18 to the states of Arkansas, Louisiana, Mississippi and Tennessee to control tarnished plant bug in cotton. At the time of the authorizations, EPA had reviewed over 400 sulfoxaflor studies with the goal of ensuring public health and ecological protections and determined that the use would not cause unreasonable adverse effects on the environment. In addition, EPA reviewed the applications and supporting documentation for the section 18 requests and concurred with the governments of AR, LA, MS and TN, that emergency conditions existed for a number of growers in these states and that their cotton crops were facing significant economic loss. Thus it is not correct to state that sulfoxaflor was "unevaluated" before the emergency exemptions were issued.

EPA is unaware of any adverse incidents associated with the section 18 use in 2012. A University of Tennessee Professor of Entomology and Plant Pathology commented that he "received no reports of performance failures, secondary pest outbreaks, bee kills or other negative effects." (see #2 above, comment 0160). The Louisiana Department of Agriculture and Forestry and the Mississippi Department

[29] USEPA. 2012. Sulfoxaflor; Pesticides Tolerances for Emergency Exemptions. EPA-HQ-OPP-2012-0493; FRL-9361-4. Federal Register/Vol 77 No. 189.

of Agriculture and Commerce informed the Agency that they received no calls, heard no complaints, and were not requested to conduct any investigations.

Regarding the comment that EPA issued tolerances for sulfoxaflor residues in cotton commodities associated with the section 18 use and that these tolerances create environmental risks to bees, EPA notes that the matrices related to bees are completely different from matrices for cotton related to human consumption (e.g. through use of cotton forage for livestock). Residue trials conducted to establish tolerances for residues on fruit and vegetables, etc., follow the use pattern of the proposed label – which includes a pre-harvest interval (PHI). The PHI is the amount of time a pesticide may be applied to a crop prior to harvest. PHIs are used to ensure that residues are at or below tolerance levels by the time a commodity is distributed in commerce. The PHIs for sulfoxaflor range from 1 day to 14 days. Application of a pesticide to a crop within as little as one day of harvest would be expected to result in higher residues than what would be seen in nectar and pollen from the bloom period of that crop. Additionally, the derivation of these two residue thresholds (tolerance and bee residue in nectar) are completely different in terms of the exposure and toxicological basis and are not expected to be similar. Further, the residue in (on) a fruit may have very little relationship to that nectar. The mitigation measures taken should ensure exposure below this value for indeterminate blooming crops. The human health tolerances have no direct bearing on pollinator protection.

The FIFRA Emergency Exemption program has long supported the beekeeping industry. More section 18 authorizations have been issued to help beekeepers than have been issued to any other group. In fact, section 18 exemptions for the use of the unregistered chemical "Hop beta acids" have been authorized to help beekeepers in at least 34 states for the past 3 years. Without EPA's ability to authorize emergency use of unregistered pesticides, beekeepers themselves would be denied access to a tool to control varroatosis or to any other proposed new active ingredient that may assist in combating this pest.

5) Threats to bees and submitted pollinator study issues

Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384): Neonicotinoids affect the nervous system of insects, causing irreversible blockage of the postsynaptic nicotinergic acetylcholine receptors (nAChRs) (via a selective agonistic mechanism).[30] Chemicals that disrupt the nAChRs - which play roles in many cognitive processes - lead to disruptions in the nervous system. In honey bees this includes disruptions in mobility, navigation, and feeding behavior.[31] Lethal and sublethal exposures have been shown to decrease foraging activity, along with olfactory learning performance and decreased hive activity.[32] Sulfoxaflor also disrupts the functioning of the nAChRs and symptoms in honey bees will be the same as seen with neonicotinoids, i.e. disruption in mobility, feeding and learning behavior.

Sulfoxaflor induces high mortality among honey bees from zero to three days post application. According to EPA's Honey Bee Risk Assessment, on average the mortality rate was as high as seven to 20 times that of controls during the first three days after application (at 3-67% of US maximum application rate). Declines in flight intensity were also observed. While recognizing the high acute toxicity of sulfoxaflor, EPA rationalizes that these effects, which include behavioral abnormalities, are "short-lived." Incredibly, it seems EPA believes that the high incidence of bee death following short-term exposure from sulfoxaflor does not factor in the long-term effects on brood and colony

[30] USEPA. 2011. BEAD Chemical Profile for Registration Review: Clothianidin (044309). Federal Register Docket Id. No.: EPA–HQ–OPP–2011– 0865

[31] Desneaux, N. et al., 2007. Sublethal Effects of Pesticides on Benefical Anthropods. Annual Review of Entomology, 52:81-106

[32] Decourtye, A. et al., 2004. Effects of imidacloprid and deltamethrin on associative learning in honeybees under semi-field and laboratory conditions. Ecotoxicology and Environmental Safety.57: 410-419

health. However, when all or most of foraging bees are dead within three days of sulfoxaflor exposures, a long-term threat to bee colonies becomes significant, not to mention economic impacts on beekeepers who have lost the viability of hundreds of hives within a three day period.

Similarly, EPA states that "the effect of sulfoxaflor on honey bee colony strength when applied at 3-32% of the US maximum proposed rate was not apparent in most cases." However, an evaluation of effects at higher rates, but within the U.S. maximum (e.g. 75% US max. proposed rate) does not seem to be known and presents a data gap. Additionally, many of the industry studies EPA reviewed for its honey bee risk assessment contained limitations, with some results being interpreted "with caution" due to statistical weaknesses, inconsistencies with controls and design, resulting in many results being considered "inconclusive." This is especially apparent for studies examining brood development. These inadequate, "flawed" studies that lack definitive data are the basis of EPA's decision for granting registration to sulfoxaflor. Clearly, the information from these studies cannot support a sulfoxaflor registration.

Honey bee acute oral and contact LD50 values for sulfoxaflor are 0.05 and 0.13 µg a.i./bee, respectively, as determined by the agency. In many of the industry residue studies reviewed by EPA, sulfoxaflor residues in nectar were on average less than 0.07ppm. EPA states that this is the threshold value for oral and contact exposures that would not exceed levels of concern, based on the agency's calculations. Given that there is little independent data available that measures real-world sulfoxaflor residue levels, the agency does not have meaningful data to support that residues would occur less than 0.07ppm in nectar. To address this uncertainty, EPA has proposed to reduce the application rate of sulfoxaflor from the requested 0.133lbs a.i./acre to 0.09lbs a.i./acre and increase the minimum spray interval, in order to mitigate pollinator risks. EPA believes in doing so, residues in nectar would not exceed 0.07ppm. The agency also believes applications of sulfoxaflor at this 'reduced' rate would not result in brood loses or impact long-term colony health during the time period required for the conditional studies to be performed and assessed.

The agency's attempts to mitigate risks to honey bees highlight the real deficiencies in the agency's risk assessment process. Risk assessment approaches have historically underestimated real-world risks and attempts to mitigate adverse impacts with measures that prove insufficient and impractical. These risk assessment approaches make determinations that the risks are "reasonable," while failing to take into account numerous circumstances and realities that make honey bees vulnerable to chemical exposures including user failure to adhere to application rate guidelines, and local environmental conditions that may predispose crops, and other plants, to accumulate higher chemical residues, especially in nectar and pollen. In fact, EPA is just now requesting a residue study to assess the nature and magnitude on residues in a pollinator-attractive crop, further illustrating that risk estimates considered in making conclusions in this honey bee risk assessment are unreliable, and most likely will not reflect real-world scenarios, putting bees at risk. The agency must instead utilize a *precautionary approach* and wait until all the relevant data can be evaluated with respect to honey bees and other organisms before considering a sulfoxaflor registration and allowing this chemical into the environment.

National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369):
Although honey bee losses can be caused by a number of factors, pesticide exposure is a common theme that is both central to and integrally related to colony failures. There is no question that acute poisonings regularly kill colonies. Persistent insecticides with extended residual times applied to blooming crops continue to cause acute poisonings for pollinators for several weeks after application.

Acute kills where piles of dead bees are found are immediately obvious, but we also notice major colony declines after exposure to pesticides. Sometimes these losses appear a week after the spray

event or even several months later. It is more difficult to document the precise fraction of losses that may be attributable to these sublethal effects of pesticides, but there is strong evidence of a connection. Even at the relatively low concentrations of systemic pesticides that honey bees are typically exposed to in pollen and nectar through normal foraging, research has shown that these pesticides can cause impaired reproduction and reduced queen survival (making it difficult for colonies to thrive and reproduce),[33] impaired immune function (making the bees more susceptible to pathogens),[34] disruption of hive communications (reducing the efficiency of the hive),[35] and decreased homing abilities that result in loss of foragers.[36]

The use of systemic insecticides has increased over time, as registered uses have expanded. In some parts of the country (the Midwest in particular), there is no safe place for a bee to be, with little available forage that is not contaminated with these systemic pesticides. Sulfoxaflor is a similar systemic insecticide that would further compromise the availability of clean bee forage.

The conditional registration of sulfoxaflor would add another highly acutely toxic insecticide that would be applied to blooming crops that are attractive to honey bees, like cotton, citrus and fruiting vegetables. The toxicity data clearly show that sulfoxaflor is highly acutely toxic to bees, but information on the sublethal effects is lacking. Without sufficient information on these effects that have been shown to be problematic for other systemic pesticides, US EPA should not conditionally register sulfoxaflor.

National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369): BEAD concludes that simply waiting to spray until bees are not present will prevent losses and assumes that only acute poisonings will cause losses; however, the studies that are available in the docket suggest that sublethal exposures can adversely affect colony health over the long term. The BEAD analysis does not address the fact that sulfoxaflor will be taken up systemically by the plant and be expressed in the nectar, leading to longer-term exposure to the chemical. An assessment of the amount of pesticide to which pollinators would be exposed over time and the risk it poses to colony survival is unaddressed.

Thomas R. Smith's comment (Docket # EPA-HQ-OPP-2010-0889-0342): My evaluation of the toxicity studies leads me to conclude that the conditional registration of Sulfoxaflor will result unacceptable damage to honeybee colonies. My conclusions are based on the following:

1. The Semi Field Tunnel Study No.1 indicates the mortality of bees exposed to direct contact of Sulfoxaflor at the rate of 99 g ai/ha experienced a 7X mortality rate compared to controls. The tested 99 g ai/ha. This 7X mortality is quite close to the 10X mortality rate for Dimethoate.

2. The label recommendation for cotton of 150 g ai/ha is 33% higher than the 99 g ai/ha tested in the Semi Tunnel Study. In addition, the label will allow for two (2) treatments of 150 g ai/ha. This will expose pollinators to 133% the tested rate twice within a relative short period of time thereby compounding the effects upon the hive.
3. Residues levels exceeding 2,000 ppm in pollen and nectar were observed after two, (2),

[33] Tasei JN. 2001. Effects of insect growth regulators on honey bees and non-Apis bees. A review. *Apidologie* 32:527–546.

[34] Desneux N, Decourtye A, Delpuech J-M. 2007. The sublethal effects of pesticides on beneficial arthropods. *Annu.Rev. Entomol*. 52:81-106.

[35] Medrzycki P, Montanari R, Bortolotti L, Sabatini AG, Maini S, Porrini C. 2003. Effects of imidacloprid administered in sub-lethal doses on honey bee behaviour. Laboratory tests. *Bulletin of Insectology* 56: 59–62.

[36] Henry M, Béguin, M, Requier F *et al.* 2012. A common pesticide decreases foraging success and survival in honey bees. *Science* 336:348–350.

treatments at 0.134 lb ai/ha up to 10 days after treatment. This indicates a long period of exposure to adult bees and brood will occur at the recommended rate for cotton.

4. Studies do not indicate how these levels may affect the life span of the adult bee or the brood reared under continuous pressure of Sulfoxaflor. Studies also do not indicate how exposure affects the natural immunity to diseases and pests of the adult bee or brood raised under this condition. Recent studies have concluded that pesticide exposure has resulted in reduced honey bee fitness. The studies don't document adequately how the colony as an organism itself will be affected in its ability to communicate and achieve the necessary functions of effectively gathering pollen and nectar. Studies do not measure the ability of bees to produce royal jelly with adequate nutritional value and over the accepted period of life span to maintain the colony population dynamics. Studies do not measure the effects from Sulfoxaflor exposure to maintain hive temperatures in the short term or delayed long abilities. The colony viability can completely fail simply by its inability to precisely regulate temperature and humidity within the hive.

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): A major issue with the proposed conditional registration of sulfoxaflor is that the pollinator studies submitted were incomplete and inconclusive. The current commercial neonicotinoids have been shown to have severe adverse impacts on honey bees and other non-target insects, which furthers concerns about the use of sulfoxaflor. Over the past decade, honey bee colonies nationwide have suffered record annual losses of typically about 30% to upwards of 90% in worst case situations. Pesticides have recently been identified as a primary contributing factor in these alarming population losses. Introducing yet another systemic, highly toxic insecticide to bee populations will only exacerbate these problems, contribute to the loss of beekeeper livelihoods, damage the agricultural economy, and threaten the diversity of our nation's food supply. Synergistic effects of sulfoxaflor and other stressors (additional pesticides, parasites, etc.) have also not been addressed. It is crucial to examine the realistic uses of sulfoxaflor and assess its impacts in light of the environmental stressors already faced by pollinator populations. Given the uncertainties and initial results that point to significant acute hazards, sulfoxaflor presents unreasonable adverse effects to bee species.

Studies on individual bees (Tier I) showed that sulfoxaflor is highly acutely toxic to honey bees, but further Tier II studies were incomplete or methodologically flawed. This lack of information about honey bee toxicity is an unacceptable data gap that should prevent the registration of sulfoxaflor. EPA notes several concerns with the reliability of the Tier 1 data, including:

- use of maximum residue reported in pollen and nectar to represent exposure to all bee castes and all crops
- lack of chronic toxicity data for adult and larval bees (and longer-term exposure to pupae)
- selection of the toxicity endpoint from the larval toxicity test
- accuracy of consumption rate estimates used for various bee castes
- variation in pesticide residues in pollen and nectar
- conservation of pesticide dose from plant tissue to the hive[37]

The formulated material was three times more toxic to adult bees than the technical material and the oral toxicity was even higher.[38] Measured residues of sulfoxaflor in pollen at field-application rates are three orders of magnitude (1,000-times) higher than that for imidacloprid (up to 7ppm SFX versus

[37] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 91.

[38] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration: Appendix D, Supporting Information for Honey Bee Risk Assessment. Docket ID: EPA-HQ-OPP-2010-0889-0026.

5ppb for IMD), resulting in a high adult acute risk quotient that is unacceptable.[39] [40] Presence in pollen and nectar ensures that developing bees will be orally exposed, yet no clear evaluation of this toxicity has been done to date. Larval toxicity was slightly lower than for adults, yet real impacts on honey bee individuals and colonies under field conditions remain unknown. The chronic toxicity endpoints for adult and larval bees are missing because of limitations in the study design that precluded the use of results beyond day seven.[41] This list of uncertainties and deficiencies associated with the Tier 1 studies should be cause enough to preclude EPA from approving sulfoxaflor, but there are additional problems with the submitted semi-field studies.

EPA does not have an approved field study protocol; thus the agency has no valid field studies on which to evaluate SXF toxicity to honey bee colonies. Of the semi-field studies that were submitted, five of the six were conducted with less between 3% and 67% of the proposed maximum label rate for the US.[42] Without trials conducted at field-realistic exposure levels, EPA has no data to determine how bees, both individuals and colonies, will be affected by sulfoxaflor use. Even at the low doses that were evaluated, significant adult mortality on the day of spray application was observed, so while it is certain that higher doses will produce greater mortality, the extent of this toxicity has never been evaluated. Thus, EPA has no data on the maximal field exposure rate impacts on honey bees or any other pollinator on which to base a conditional registration. Brood and long-term colony health studies were not included or were unacceptable methodologically, compounding the unknown potential long-term chronic effects of sulfoxaflor. The long term stability and persistence of the compound indicates that chronic effects on hive populations will occur. Without information on realistic exposures, the risks associated with field usage cannot be dismissed or deemed acceptable. The evidence from the pollinator studies points to unreasonable adverse effects to honey bees, which precludes EPA from approving the conditional registration.

EPA's response:

A. Beyond Pesticides. *Sulfoxaflor results in high incident of bee death, with all or most of forager bees dead after three days. This will result in a long-term threat to bee colonies*

Agency Response. Additional information is provided here to clarify the observed mortality pattern resulting from sulfoxaflor exposure in the submitted semi-field studies. For example, the following graph shows the daily mortality pattern observed from one of the tunnel studies that evaluated the highest application rate currently proposed (0.086 lb a.i./A), the negative control, and the positive control (dimethoate). In this and other tunnel studies, bees are forced to feed on only treated crop inside the tunnel enclosures and product is applied when bees are actively foraging. Daily mortality in the sulfoxaflor treatment (red bars) spikes on the day of application and returns to control levels by day 3. Relative to control mortality, 488 additional bees died in the highest sulfoxaflor treatment, which represents 7% of the total hive strength in this treatment. Contrary to the comment, this magnitude of mortality does not represent all or the majority of forager bees present in the hive. Rather, it is considered to be well within the assimilative capacity of the hive due to the compensatory mechanisms that exist in honey bee colonies. This general pattern of short-term increases in mortality followed by a return to control mortality rates within 1-3 days was consistent across the other tunnel studies conducted with sulfoxaflor. In

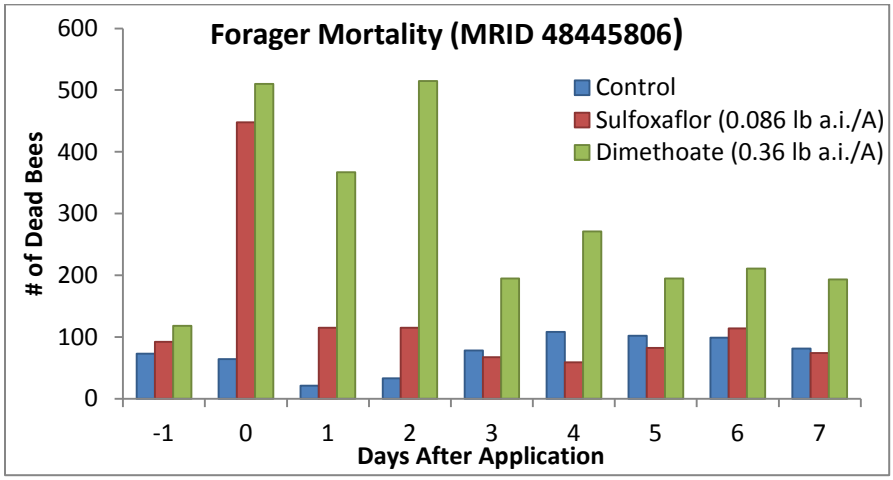
[39] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 84.

[40] Chauzat MP, et al. 2011. An assessment of honeybee colony matrices, *Apis mellifera* (Hymenoptera: Apidae) to monitor pesticide presence in continental France. *Environ Toxicol Chem.* 30(1): 103-111.

[41] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 92.

[42] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 11.

contrast, the mortality pattern observed from the reference toxicant (dimethoate) is much larger in magnitude and in duration compared to sulfoxaflor. Notably, the reference toxicant is added in order to document that the pesticide application results in exposure to bees and that adverse effects can be detected in the study.



B. Beyond Pesticides. *Information on sulfoxaflor effects at maximum application rate represents a data gap. This data gap and the limitations in tunnel studies (statistical weaknesses, control and design inconsistencies, many inconclusive results) are insufficient to support the registration of sulfoxaflor.*

Agency Response. The Agency's ecological risk assessment was based on an assumed maximum single application rate of 0.133 lb ai/A. However, this maximum allowable rate was subsequently lowered to 0.086 lb ai/A in order to reduce potential exposure to bees and other insect pollinators. At this lower rate, only 2 of the 66 measurements of sulfoxaflor residues in forager-collected nectar from the cotton semi-field study (MRID 48755606) exceeded 0.07 ppm, which is the residue value that corresponds to the acute risk level of concern (LOC=0.4) for adult forager bees (see **Figure A** below). Forager bees represent the caste of bees that is most exposed via nectar. These two values of sulfoxaflor in forager-collected nectar (0.073 and 0.127 ppm) both occurred within the first day after application and correspond to acute risk quotients of 0.4 and 0.7, respectively. These risk quotients are very close to the Agency's acute risk level of concern of 0.4. Similar to the residue findings for sulfoxaflor in nectar, results of sulfoxaflor measurements in forager-collected pollen show that all but 1 of the 66 samples are below 2.5 ppm, which is the residue value that corresponds to the acute risk LOC of 0.4 for adult nurse bees (**Figure B,** below). Nurse bees represent the caste of bees that is most exposed via pollen. Thus, 97% of the sulfoxaflor residues measured in forager-collected nectar and 98% of the residues measured in forager-collected pollen from the cotton semi-field study are below the Agency's acute risk level of concern. No exceedance of this residue-based LOC threshold in pollen occurred in the other three studies which quantified sulfoxaflor residues in pollen and nectar (MRID 48476601; 48445806; 48755601). Only one exceedance of the residue-based LOC threshold in nectar occurred in these same three studies, and this value (0.09 ppm) was very close to the residue-based threshold of 0.07 ppm.

In considering these results from the Tier 1 risk assessment for bees included in the ecological risk assessment document, it is important to recognize that conservative measures of exposure were used. Specifically, the highest recorded residues of sulfoxaflor in pollen and nectar are the

bases of its Tier 1 risk assessment. Further conservatism was introduced by assuming that foragers would be exposed to a continuous dose at these maximum residue concentrations and no reduction in pesticide dose would occur based on its transport and processing over time and its storage within the hive. It is also important to note that the potential risk to other castes of bees is even lower due to their much lower consumption rates of pollen and nectar. In summary, the Tier 1 risk assessment for bees indicates that nearly all of the sulfoxaflor residues measured in pollen and nectar are below the acute risk LOC and those few measurements that exceed the LOC do so by a small margin. Given the level of conservatism associated with the acute risk LOC recently identified by the FIFRA SAP[43], the Agency considers the results of the Tier 1 risk assessment to indicate overall low acute risk to bees via consumption of contaminated pollen and nectar. It is further noted that the Tier 1 risk assessment does not incorporate any of the mitigation measures put forth on the sulfoxaflor label. These include restrictions that the product must not be applied 3 days prior to bloom, during bloom, or until petal fall for the majority of crops. For the remaining bee-attractive crops, advisory language to notify known beekeepers of scheduled application and to conduct those applications in early morning or late evening has also been added to the labels. These risk mitigation measures will further reduce exposure of bees to contaminated pollen and nectar in addition to avoiding exposure from direct contact with pesticide spray droplets. The Agency recognizes, however, that the studies supporting the Tier 1 risk assessment do not include effects from chronic exposures. This reflects a limitation in Tier 1 toxicity studies for bees that is common to all pesticides. Chronic effects are therefore included in the Tier 2 studies.

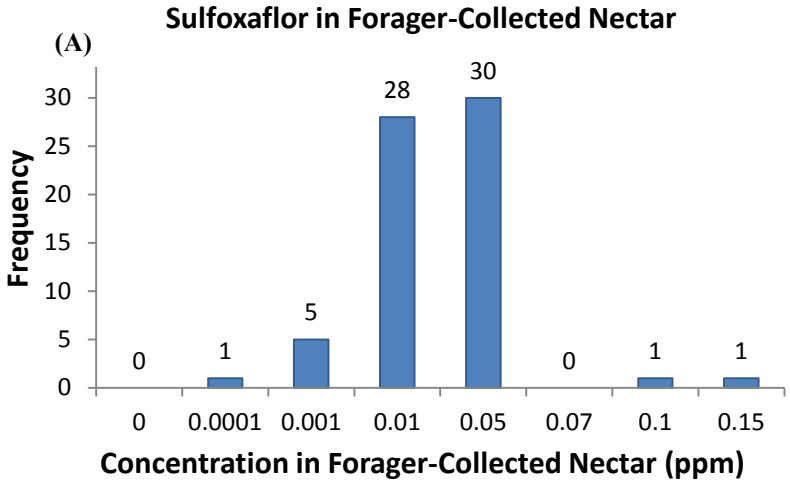
Regarding the limitations associated with the submitted Tier 2 studies in its risk assessment for sulfoxaflor, the Agency notes that these limitations were articulated in the sulfoxaflor ecological risk assessment document. Importantly, however, results from the Tier 2 semi-field (tunnel) studies represent 'worst case' exposure conditions for bees from both contact and oral exposure routes. Even with these worst case conditions, impacts on forager bee survival, flight activity and bee behavior were shown to be short lived (lasting 1-3 days). Such impacts in the natural environment are likely to be less than those observed in the semi-field tunnel studies due to bees obtaining pollen and nectar from sources other than the treated field.

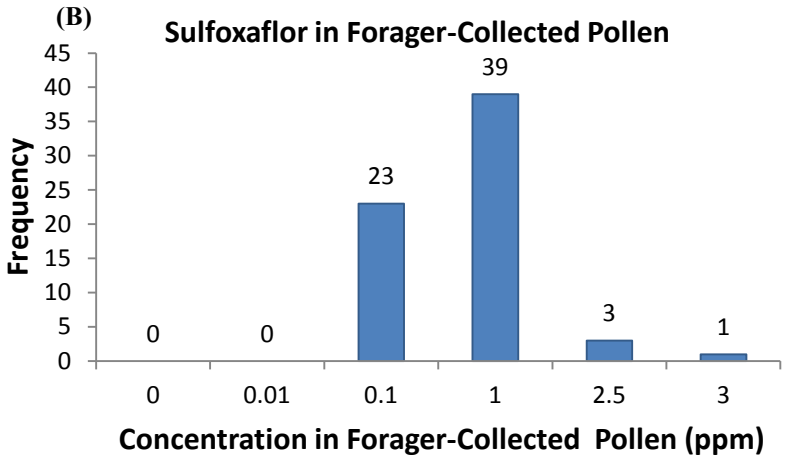
Although statistical weaknesses were documented for these studies, the Agency did not rely exclusively on statistical interpretation of results in its risk findings. Rather, it relied on its best professional judgement in evaluating the magnitude and duration of effects from these studies. Therefore, the Agency believes that the statistical weaknesses did not materially compromise its interpretation of the study results. Furthermore, the statistical weaknesses noted in the sulfoxaflor Tier 2 studies are common to all semi-field studies due to practical constraints on the number of replicates that can be incorporated into the study design.

Finally, the Agency notes that the inconclusive findings from the submitted Tier 2 studies were limited to evaluation of brood development in three studies. Evaluation of brood development was considered acceptable in one tunnel study, although this was at a lower application rate (0.043 lb a.i./A). Furthermore, measures of colony strength did not demonstrate a treatment-related affect with sulfoxaflor in the Tier 2 semi-field studies. Although results from longer-term tunnel studies conducted at the current maximum single application rate of 0.086 lb a.i./A are desirable for confirming the results of the Tier 1 risk assessment, the Agency believes that when results of Tier 1 and the proposed mitigation measures are considered, the existing limitations in

[43] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0543-0047

the Tier 2 studies do not preclude registration of sulfoxaflor given the mitigation measures (such as reduced application rates and increased minimum spray intervals) that are included on the label and the benefits provided by sulfoxaflor. Sulfoxaflor targets pests of significant of economic importance, including the tarnished plant bug threat to cotton which resulted in emergency situations in several states, as well as the Asian citrus psyllid which vectors Huanglongbing disease, the citrus greening disease, which presents an extremely serious threat to the entire Florida citrus industry. Additional pests such as the wooly apple aphid and whiteflies that have rapidly developed resistance to other insecticides will be vulnerable to the new mode of action provided by sulfoxaflor.





C. Beyond Pesticides. *The Agency has not taken into account that risk assessments historically have under estimated real world risks and that mitigation measures have proven insufficient or impractical. Further, the Agency fails to take into account numerous circumstances and realities that make honey bees vulnerable to chemical exposures including user failure to adhere to application rate guidelines, and local environmental conditions that may predispose crops, and other plants, to accumulate higher chemical residues, especially in nectar and pollen.*

Agency Response. The Agency notes that the submitted semi-field studies do take into account a number of environmental factors which may affect exposure and effects of sulfoxaflor to bees.

Such factors include temperature, humidity, precipitation, and characteristics of the treated crop and soils that all may affect exposure of bees to pesticides and subsequent effects. Furthermore, the semi-field studies confine hives and bees in tunnels during pesticide application. Therefore, they are considered to represent a reasonable 'worst case' exposure scenario in terms of maximizing the potential exposure of bees to pesticides via contact and oral routes. Regarding the overall nature of EPA risk assessment, the Agency believes that its ecological risk assessment process (and in particular that recently developed for bees) is appropriately conservative and reflects the current state of the science. Furthermore, risk mitigation measures such as preventing pesticide application during bloom are considered effective measures at reducing exposure and overall risk to bees from pesticide application. . For the recent Section 18 Emergency Use of sulfoxaflor on cotton, the Agency notes that no incidents involving bees (or other taxa) were reported to the Agency. The Agency notes that the commenter did not provide any evidence or examples to support their claims regarding EPA's risk assessment process and risk mitigation measures. This prevents the Agency from responding in more detail.

D. Beyond Pesticides. *The Agency is just now requesting a residue study to assess the nature and magnitude on residues in a pollinator-attractive crop, further illustrating that risk estimates considered in making conclusions in this honey bee risk assessment are unreliable.*

Agency Response. The comment that the Agency is just now requesting a study on the nature and magnitude of sulfoxaflor residues in a pollinator-attractive crop is not accurate. Two such studies were required as part of the application for registration for sulfoxaflor (Cotton MRID 48755606 and Pumpkin MRID 48755601). Results from these two studies supported the Tier 1 risk assessment for bees. In addition, residue data were also available from two studies with *Phacelia* (MRID 48445806 & 48476601). Notably, all three crops included in these residue studies are considered pollinator attractive.

Specifically, over 600 samples of pollen, nectar, plant tissue and bees were collected and measured for sulfoxaflor among four studies and three species of plants (Cotton, Pumpkin, *Phacelia*). A breakdown of this information is provided below. OPP acknowledges that variation in residues can be expected for different crops and use patterns. To account for this variation, OPP selected the *highest* sulfoxaflor residues measured in pollen and nectar among all the available residue data as the basis of its Tier 1 risk assessment, rather than selecting an average value or a 90th percentile.

Species	**Matrix**	**No. of Samples Analyzed**	**Application Rates in lb a.i./A (No. different rates)**	**Reference**
Cotton	Plant pollen	52	0.045 – 0.134 (4)	48755606
	Forager pollen	102		
	Forager nectar	104		
	Comb pollen	83		
	Comb larvae	112		
Pumpkin	Plant pollen	24	0.022 0.089 (2)	48755601
	Plant nectar	13		
	Plant leaf	24		
	Plant nectary tissue	24		
	Plant stem	24		

Phacelia	Comb pollen	6	0.006 – 0.088(5)	48445806
	Plant flowers	6		
Phacelia	Plant pollen	15	0.021-0.043 (2)	48476601
	Plant (whole)	15		
Total Samples		**603**		

The Agency's proposed request for one additional residue study was intended as confirmatory data with respect to the findings from the residue studies for the other three crops (cotton, pumpkin and *Phacelia*). After reconsidering the overall weight of the evidence and the statutory requirements with conditional pesticide registrations, the Agency believes the existing data for sulfoxaflor are sufficient to support its registration decision in accordance with the FIFRA standard, despite some uncertainty in the currently available residue data for sulfoxaflor.

E. Beyond Pesticides. *Sulfoxaflor is a similar systemic insecticide that would further compromise the availability of clean bee forage.*

Agency Response. The Agency agrees that sulfoxaflor is a systemic insecticide; however the Agency disagrees that available information indicates its use in accordance with the proposed label will result in unacceptable adverse effects on bees for reasons stated in response to comment #5.B above. Furthermore, the available information on sulfoxaflor residues in pollen and nectar indicates it dissipates relatively rapidly, with the vast majority of pollen and nectar DT_{50} values determined to be 3 days or less. Therefore, the Agency believes that the available information indicates the proposed uses of sulfoxaflor, in combination with its specified risk mitigation measures, would not compromise the quality of forage sources to bees.

F. Beyond Pesticides. *The toxicity data clearly show that sulfoxaflor is highly acutely toxic to bees, but information on the sublethal effects is lacking. Without sufficient information on these effects that have been shown to be problematic for other systemic pesticides, US EPA should not conditionally register sulfoxaflor.*

Agency Response. As indicated in its ecological risk assessment, sulfoxaflor is classified as highly acutely toxic to bees. At the Tier 1 level, the Agency and its FIFRA Scientific Advisory Panel both recognize that existing laboratory toxicity tests with bees do not include a rigorous quantification of sublethal effects and that additional research is needed in order to identify and incorporate appropriate sublethal endpoints into standard test guidelines[44]. However, the Agency notes that the Tier 2 studies submitted for sulfoxaflor include measurement of sublethal effects (forager flight activity and abnormal behavior). In these studies, the effect of sulfoxaflor on these sublethal endpoints was limited to brief time periods after application and returned to levels comparable with controls within 3 days. The Agency also notes that the effects quantified in the submitted Tier 2 tunnel studies (e.g., colony strength) incorporate the combined impact of sublethal and lethal effects experienced by bees. Thus, while sublethal effects other than flight activity and abnormal behavior are not explicitly quantified in the Tier 2 studies, the overall impact of sublethal effects is reflected in the overall measures of colony health quantified in these studies. Therefore, the Agency believes that the Tier 1 and Tier 2 studies submitted for sulfoxaflor with respect to bees reflect the current state of the science regarding standard toxicity test guidelines for bees and are adequate to support a registration decision in accordance with the FIFRA regulatory standard.

[44] available at: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0543-0004 and http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0543-0047

G. National Pollinator Defense Fund. *Persistent insecticides with extended residual times applied to blooming crops continue to cause acute poisonings for pollinators for several weeks after application.*

> **Agency Response.** The Agency notes that no specific information was provided to support this comment. Generally, however, the Agency notes that sulfoxaflor does not have an extended residual time for toxicity (foliar residual toxicity is < 3 hrs). In addition, the available information indicates sulfoxaflor residues are expected to dissipate relatively rapidly in pollen and nectar based on the vast majority of DT_{50} values determined to be 3 days or less.

H. Thomas R. Smith: *My evaluation of the toxicity studies leads me to conclude that the conditional registration of Sulfoxaflor will result unacceptable damage to honeybee colonies. Specifically:*

(1) The Semi Field Tunnel Study No.1 indicates the mortality of bees exposed to direct contact of Sulfoxaflor at the rate of 99 g ai/ha experienced a 7X mortality rate compared to controls. The tested 99 g ai/ha. This 7X mortality is quite close to the 10X mortality rate for Dimethoate.

> **Agency Response.** As addressed in the response to comment #5.A. above, the increase in forager bee mortality from exposure to sulfoxaflor is short-term in duration (< 3 days relative to controls) across all the available tunnel studies. This is in contrast to the prolonged increase in mortality observed for the dimethoate reference toxicant. The increase in mortality from the 99 g a.i./ha (0.086 lb a.i./A) represents 488 bees or 7% of the total hive strength. Given the worst case exposure conditions of this and other tunnel study, the low overall mortality rate observed with sulfoxaflor at the current maximum rate, and the risk mitigation measures put forth for most of the crops, the Agency believes that results from this study do not pose an unreasonable risk to bees.

(2*) The label recommendation for cotton of 150 g ai/ha is 33% higher than the 99 g ai/ha tested in the Semi Tunnel Study. In addition, the label will allow for two (2) treatments of 150 g ai/ha. This will expose pollinators to 133% the tested rate twice within a relative short period of time thereby compounding the effects upon the hive*.

> **Agency Response.** The maximum label rate of sulfoxaflor on cotton was reduced to 0.07 lb a.i./A. As indicated in the response to comment #5.B above, available information indicates the Agency low overall risk to bees from exposure to residues in pollen and nectar resulting from this application rate. Furthermore, the shortest reapplication interval is 5 days, for cotton; the reapplication intervals of the remaining crops have been increased and range from 7-14 days.

(3*) Residues levels exceeding 2,000 ppm in pollen and nectar were observed after two treatments at 0.134 lb ai/ha up to 10 days after treatment. This indicates a long period of exposure to adult bees and brood will occur at the recommended rate for cotton.*

> **Agency Response.** The Agency notes that on occasion, residues in pollen exceed 2 ppm (not 2000 ppm as indicated). As indicated in the response to comment #5.B above, only two of the 66 residue samples in forager collected pollen exceeded 2.5 ppm which is the acute risk LOC of 0.4 at application rates up to the current maximum of 0.086 lb a.i./A. Furthermore, available information indicates the sulfoxaflor residues are expected to dissipate relatively rapidly in pollen and nectar based on the vast majority of DT_{50} values determined to be 3 days or less at or below the current maximum application rate.

(4) *Studies do not indicate how these levels may affect the life span of the adult bee or the brood reared under continuous pressure of Sulfoxaflor in addition to other effects related to hive condition, pollen and nectar gathering, bee immune function, behavior, communication*.

Agency Response. The Agency believes that bees will not be faced with continuous pressure of sulfoxaflor due to the risk mitigation measures being implemented which avoid periods of bloom for most crops and daily time periods when bees tend to forage most actively. Additionally, retreatment intervals have been lengthened for many crops. Furthermore, available data indicates that residues are not likely to persist for long periods in pollen and nectar at levels of concern for bees. Regarding the other colony-level endpoints suggested for consideration, the Agency notes that most of these are integrated into measures of overall colony health (e.g., hive strength and brood development). Furthermore, the Tier 2 tunnel studies are designed to maximize exposure to bees from contact and oral exposure routes. The Agency notes, however, that long-term observations of colonies following sulfoxaflor application in tunnels were not available at the current maximum application rate of 0.086 lb a.i./A.

I. **Center for Food Safety.** *The current commercial neonicotinoids have been shown to have severe adverse impacts on honey bees and other non-target insects, which furthers concerns about the use of sulfoxaflor.*

Agency Response. Sulfoxaflor will have no greater impact than other insecticides currently used for pest control. It must be considered that sulfoxaflor is not classified as a neonicotinoid and as such comparison solely to neonicotinoids is inappropriate. Sulfoxaflor use will primarily displace use of existing less effective insecticides which have an activity profile which is similar to or worse than sulfoxaflor against honey bees and non-targets. These include not only neonicotinoids but also synthetic pyrethroids, organophosphates, and carbamates (carbaryl and oxamyl). As shown in UC Pest Management Guidelines for cucurbits (http://www.ipm.ucdavis.edu/PMG/r116900311.html), the generality that neonicotinoids have inherently greater adverse impact on non-targets is not correct. For honey bees alone, neonicotinoid impact is both a function of formulation and application rate. However, other insecticides have similar impacts to neonicotinoids to both honey bees and non-targets. Furthermore, use of a more effective insecticide, such as sulfoxaflor, can provide longer pest control at levels which are not conducive to economic loss economic threshold level and decrease the number of insecticide applications necessary for crop production. Fewer applications of insecticides could potentially have a positive impact on both honey bees and non-targets. Finally, the EPA agrees that the number of managed colonies in the US has declined over time, but this decline cannot be specifically linked to the registration of the neonicotinoids.
Occurrence of adverse incidents is low and include acute incidents from fugitive dust from planting of treated seed. Sulfoxaflor is not being registered as a seed treatment, and there were no incident reports from the use of sulfoxaflor on cotton for the Section 18 Emergency Use Exemption.

J. **Center for Food Safety.** *Synergistic effects of sulfoxaflor and other stressors (additional pesticides, parasites, etc.) have also not been addressed.*

Agency Response. Regarding the assessment of honey bee exposure to multiple pesticide mixtures, evaluation of pesticide environmental mixtures to any taxa is considered beyond the scope of the ecological assessment because a myriad factors can affect exposure and effects of environmental mixtures which cannot be quantified based on the available data (USEPA,

2004[45]).Those factors include identification of other possible co-contaminants and their concentrations, differences in the pattern and duration of exposure among contaminants, and the differential effects of other physical/chemical characteristics on the exposure and effects of chemical mixtures. Evaluation of factors that could influence additivity/synergism is beyond the scope of this assessment and the capabilities of the available data to allow for a quantitative evaluation of these factors. However, it is acknowledged that not considering mixtures could over- or under-estimate risks depending on the type of interaction and factors discussed above. The pollinator assessment, however, does evaluate the risk associated with sulfoxaflor formulated products (including the inert ingredients such as surfactants that are used in formulating the active ingredient).

K. **Center for Food Safety.** *The formulated material was three times more toxic to adult bees than the technical material and the oral toxicity was even higher.*

Agency Response. The Agency's Tier 1 risk assessment for sulfoxaflor was based on the formulated product for the reasons identified in the comment.

L. Center for Food Safety. *Sulfoxaflor's presence in pollen and nectar ensures that developing bees will be orally exposed, yet no clear evaluation of this toxicity has been done to date*

Agency Response. The Agency disagrees with the commenter's assertion that it did not consider the oral route of exposure to developing bees. The Agency's risk assessment for bees considered an extensive database on the oral exposure of developing bees to sulfoxaflor, both in Tier 1 (laboratory) and Tier 2 (semi-field) studies. These studies included larval acute oral toxicity, semi-field tunnel studies, and residue studies quantifying the amount of sulfoxaflor in pollen and nectar.

M. Center for Food Safety. *The chronic toxicity endpoints for adult and larval bees are missing because of limitations in the study design that precluded the use of results beyond day seven.*

Agency Response. The lack of chronic toxicity data for adults and larvae (beyond day 7) from laboratory toxicity tests reflects the limitation in the current state of the science for bee toxicity testing. No standard protocols are available for evaluating chronic exposure to these life stages which have been validated for regulatory use. Therefore, this limitation is applicable to all chemicals, not just sulfoxaflor. Importantly, however, chronic effects on adults and larvae are evaluated using the Tier 2 semi-field studies with sulfoxaflor. Thus, in consideration of the weight of evidence concerning the magnitude and duration of sulfoxaflor residues in pollen and nectar (Tier 1) combined with the aforementioned mitigation measures and results from Tier 2, the Agency considers the available data adequate to support a registration decision in accordance with the FIFRA regulatory standard.

N. Center for Food Safety. *EPA has no data on the maximal field exposure rate impacts on honey bees or any other pollinator on which to base a conditional registration for sulfoxaflor.*

[45] USEPA. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency: Endangered and Threatened Species Effects Determinations. Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs, Washington, D.C. January 23.

Agency Response. As explained in the response to comment # 5.B., the maximum allowable rate was subsequently lowered to 0.086 lb ai/A in order to reduce potential exposure to bees and other insect pollinators. The agency has two Tier 2 tunnel studies that include this application rate and both indicate no treatment level effect on hive strength over the duration of these studies. The Agency notes, however, that long-term observations of colonies following sulfoxaflor application in tunnels were not available at the current maximum application rate of 0.086 lb a.i./A. However, given the weight of information concerning the magnitude and duration of sulfoxaflor residues in pollen and nectar combined with the aforementioned mitigation measures, the Agency considers the available data adequate to support a registration decision in accordance with the FIFRA regulatory standard. Regarding the adequacy of existing data, OPP notes that the available information on sulfoxaflor residues in bee-related matrices is actually quite extensive.

6) Bee assessment in economic analysis

National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369): Attempting to limit the time of application (both seasonal and time of day) with label statements is not effective for protecting honey bees for all pesticides and crops, and some inaccurate assumptions were made about bee behavior on specific crops. In particular:

Cucurbits: The assumptions that bees do not work the plants all day long is incorrect. Foraging activity and other honey bee activity near a treated field is dependent upon many factors including:

1) *Varietal differences in nectar production.* For example, Honey Dews and squash produce more nectar than other cucurbits, which the bees will forage on the entire day, until dark if temperatures permit.

2) *Hive placement.* The BEAD study states that the bees are at little risk because they are not working the plants in the afternoon. But the analysis does not assess the risk to the hives placed at the field edge and inside the field, which is common practice to accommodate the preferred stated 200 yard effective foraging habit. It is true that the greatest number of visits occur very near to hive. Those same bees, even if not foraging in the crop, are flying within the treatment area to access water or to forage on other nearby flowering weeds and plants. Blooming weeds are very problematic to growers in cucurbit fields because of the crop's sensitivity to most herbicides. Hand weeding costs can be as high as $100 per acre. Hand weeding culturally only occurs when the crop is young. Yet no risk was assigned to pollinators foraging in the blooming weeds in the field.

3) *Temperature.* The BEAD analysis states that bees stop working the crop in the afternoon. That is not true in areas of the west. The bees return to forage for nectar once the temperature drops and the plant begins to accumulate nectar in the blooms.

Night application of current pesticides is the most common recognized practice in cucurbits to reduce pollinator kills. It is not clear if this method will work to reduce kills from sulfoxaflor, since the data on sublethal effects are inadequate to make this determination. The data that do exist indicate that sulfoxaflor residues contaminate pollen and nectar for many days.

The results of a survey conducted in service to the EPA Pesticide Program Dialog Committee Pollinator Workgroup[46] indicated that cucurbits were responsible for some of the highest losses observed by beekeepers through acute poisonings (Figure 2). It is important for BEAD to get the facts correct in the interest of avoiding further losses. With the inadequate mitigations proposed

[46] PRI, 2012. *Survey on Acute Pesticide-Related Bee Kills.* Pesticide Research Institute. http://www.pesticideresearch.com/site/?page_id=24.

in the BEAD analysis, future acute kills from sulfoxaflor applications are highly likely.

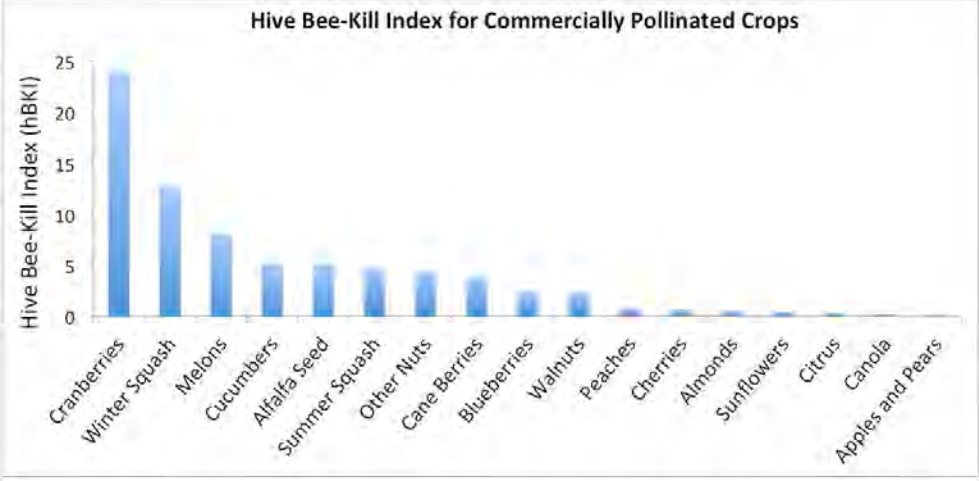


Figure 2: The hive bee-kill index is a measure of number of acute poisonings per acre of crop planted. For a detailed description of the index, see http://www.pesticideresearch.com/site/?page_id=2360/.

Cotton: The assumption that bees have only limited contact with cotton is incorrect.

1. Bees readily work cotton for nectar. This information is well documented by USDA and during the years of the Indemnity program, the cotton honey price was quoted monthly in the *American Bee Journal* and *Gleanings In Bee Culture* trade magazines up until the honey grading system changed in the late 1980's.
2. Bees are exposed to copious amounts of pollen as they enter the cotton flower to collect nectar. They return to the hive with pollen, which will remain on the body hairs. The house bees clean the worker bees of the remaining pollen on their bodies with their mouth parts. The pesticide will enter the food chain of the hive via the cleaning process that takes place inside the hive.
3. Bees do work the cotton flower and plant nectaries during late afternoon hours until dark. Bees do stop working cotton during the typical high daytime temperatures that occur in the cotton belt. However, the bees return after their afternoon Siesta and forage heavily in the late afternoons—many times and areas until dark. Late daylight afternoon applications will result in exposure to the application and the highest pesticide concentrations.
4. The effective weed control of "Roundup Ready" technology has drastically reduced blooming weeds within the field. The common use of Roundup around cotton field edges, ditches and waterways reduces the availability of forage for pollinators. This results in more intense foraging within the cotton field itself.
5. Cotton areas in which Roundup-resistant weeds have evolved present a risk from blooming weeds. Palmer Amaranth, being the most common weed to develop resistance to Roundup, is highly attractive to pollinators as a source of both nectar and pollen. These plants require pollen to be moved from the male plant to the female plant. A pollinator must do that. Fields with these Roundup-resistant blooming weeds will be VERY problematic for pollinators unless near 100% weed control is achieved. If achieved, the risk returns to the number 4 scenario.

A major flaw in the BEAD risk assessment is that it assumes that if pollination is not beneficial to the plant, the risk is low. It does not assess the risk from use of the plant by pollinators. This is clearly stated in cotton. For citrus, the assessment takes into account the use of the citrus flower by the pollinator. The practice of only allowing pesticide applications to citrus during periods of no bloom should protect pollinators if no blooming weeds are present in the field and if sulfoxaflor is not

persistent in plant tissue. However, EPA has no data that would demonstrate that either of these conditions holds true. The conditional registration of sulfoxaflor would result in managed honey bee colonies becoming the unwitting test subjects, and the beekeepers who own them would be made to pay the price if sulfoxaflor proves to be highly toxic on a sublethal basis as well.

Thomas R. Smith's comment (Docket # EPA-HQ-OPP-2010-0889-0342): The economic assessment published by EPA is unacceptable from the standpoint of establishing the benefit of managed honeybees. The assessment myopically assesses the pollinator worth solely based of the pollination benefit to the individual treated crop. The colonies exposed in the cotton field are the same colonies which will be exposed in all the other pollinated dependent crops. The assessment lacks the understanding of the relationship between managed honeybees and production agriculture. Managed honeybee colonies are moved thought the nation to meet the demands of crops requiring pollination. This fact will result in multiple exposures where crops in bloom, which has not been acknowledged nor the potential economic damage properly assessed. If a colony is damaged due to exposure on cotton to the level where it cannot be utilized to commercially pollinate crops, those crops are at risk of an inadequate supply of available pollinators and/or the additional costs of supply and demand. Simply put, it externalizes the costs onto other persons, the beekeeper and the farmer of pollination dependent crops. The growing need for pollinators in the United States is clearly establish by the RaboBank report on pollinators and should be carefully reviewed.

The economic assessment description of how honey bees are managed during the commercial pollination of crops indicates complete lack of knowledge of the actual physical and biological facts. It describes field conditions and plant physiology which are not representative. For example: Colonies are commonly placed within the field borders of most fields in order to achieve maximum pollination. The assessment states colonies are placed on field border giving justice to the recommendation for "late afternoon" application. (Whatever "late afternoon" actually is) The assessment states that nectar production ceases around mid-day in melon fields. This is incorrect and, when in fact, nectar production is dependent upon many variables including varietal type, cultural practice, weather conditions, soils and, location. In my experience, melon plants cease producing nectar during mid-day heat and begin to produce nectar again as temperatures cool later during afternoon. Bees begin to forage the flowers for nectar in the late afternoon until dark if temperature permit. Colonies can utilize the field for collection of water throughout the day. Weeds are always problematic to melon fields because of their sensitivity to herbicides. Blooming weeds are present almost without exception in melon fields. Pollinators will forage blooming weeds for pollen and nectar throughout the day until light fades or temperatures prohibit foraging. The colonies located within the field are vulnerable to exposure as the fly to forage or collect water.

I describe these short comings in the assessment to point out the fact that the assessment is focused on avoiding the obvious risk mitigation measure, which is to APPLY AFTER DARK. The assessment is unaware, based on its discussion, that SPRAYING AFTER DARK IS THE MOST ACCEPTED AND OBSERVED CUTURAL PRACTICE FOR PROTECTING POLLINATORS WHEN COMMERCIALY POLLINATING CROPS.

Several assumptions made about cotton and bees are incorrect. The assessment states that bees do not readily enter the cotton flower to collect pollen or nectar. Also stated is that cotton pollination can be improved by 3-30% based on studies. My point is: How can pollination be improved if bees do not readily enter the flower? I observe bees readily entering open cotton flowers to collect nectar. These nectaries are located at the base of the flower where the highest viability pollen also occurs. This requires the bee to press itself between the anthers and the pedals to gain access to the nectar. When the bee exits the flower, the bee is covered with copious amounts of pollen on its body. Pictures were provided to Environmental Fate and Effects Division in 2012. The bee

returns to the hive where the house bees clean the remaining pollen off the forager with their mouth parts thus providing the entry point to the hive food chain. The assessment states that bees do not work cotton for nectar or pollen in the afternoon. That is completely false for the western U. S. Bees readily reenter the cotton field in late afternoon until dark to gather nectar. Bees enter the cotton fields at first light and forage until about mid-day. As in the case for melons, the assessment goes to great extent to justify spraying in the "late afternoon" as opposed to at night when the bees are certain not to be present and exposed to direct contact or the highest toxicity levels.

Toxic levels of Sulfoxaflor on cotton will most certainly result in a great threat all pollinator due to its attractiveness to pollinators. Cotton produces much nectar and bees will fly up to 2 miles to gain access to that nectar source. The Cotton Council has promoted studies as factual stating bees don't prefer to forage on cotton "very much". Historically cotton is one of the top two problematic crops for pesticide related damage to pollinators, along with citrus. A price for cotton honey was quoted monthly in the American Bee Journal and Bee Culture trade magazines in the 1970's and 1980's. A California price and a Southern US price were quoted for cotton honey. In the 1990's the U.S. honey pricing changed from a floral/color source system to a standardized color grade system. Original copies of these trade magazines for reference.

The assessment states that applications on citrus would be best when no bloom was present because of its attractiveness to honeybees. The glaring admission of this statement is that bees are at great risk when they are "visiting", or "actively visiting" any plant in bloom. If the risk exists for citrus, the risk exists for all blooming crops. Pollinators must not be deemed expendable in one crop and not the other. They are either expendable or not expendable. NOT EXPENDABLE!

EPA's response:

The EPA's impact assessment was only intended to evaluate the potential role that sulfoxaflor may play in production of the various crops for which registration is being sought and to provide supplemental information regarding the importance of honey bees for production of these crops. BEAD's role in the assessment process is to examine whether the new pesticide meets a need that is not being met by currently registered pesticides or non-chemical alternatives and determines if the benefits from the new pesticide are greater than those from currently registered pesticides or non-chemical pest control measures. As such, BEAD only assesses the benefits of registration.

EPA agrees with the commenters that foraging activity and other honey bee activity near a treated field is dependent upon many factors. These factors will vary according to crop, variety, meteorological conditions, hive placement, etc., and therefore it is not plausible to evaluate all potential bee activity for all situations. When commercial beekeepers place hives in the field borders or directly in fields (as noted in the comments), protection of the hives is best established through the formal agreement of responsibilities between the bee keeper and the farmer. This agreement should include water availability, weed management, and other factors which the parties determine are relevant to the individual situation. It must also be pointed out, that not all weeds are attractive to honey bees. It is implausible to evaluate every weed which may be encountered in the assessed crops as their attractiveness to honey bees may vary both spatially and temporally and as a function of weed diversity in a given area. EPA does note that, in contrast to the comments regarding honey bee activity in melons until dark, collection of pollen usually ends before noon and nectar collection may continue into late afternoon (Mussen and Thorpe, University of California, publication 7224).

EPA acknowledges that honey bees do enter cotton fields. The impact assessment provides information relative to the importance of honey bees to cotton production. Based solely on the reproductive biology of cotton, EPA concluded that honey bee pollination can increase yields but is not essential for cotton production. EPA has seen no data which would indicate that use of sulfoxaflor would result in a greater detrimental impact on honey bees than the currently registered alternative insecticides. EPA also believes the additional labeling mitigation will reduce exposure to bees and therefore the potential for downstream effects would be minimized. Furthermore, availability of sulfoxaflor as an efficacious alternative insecticide could potentially reduce the impact on honey bees through a reduction in overall number of insecticide applications when based on the economic threshold component of IPM programs.

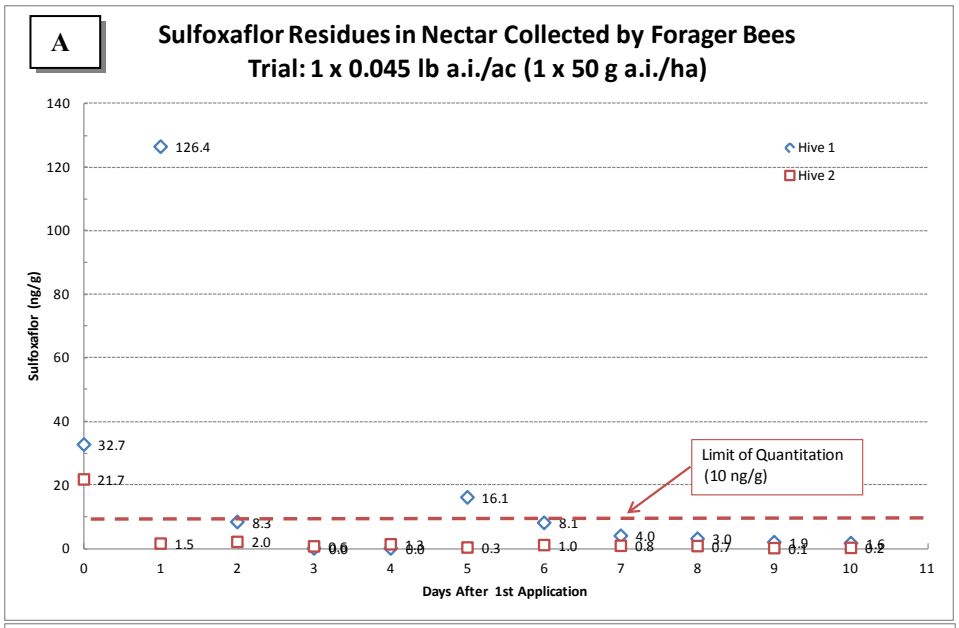
A recent review by EPA of a Section 18 Emergency Exemption for the use of sulfoxaflor on cotton, indicates that some farms in mid-south cotton production are currently applying up to 16 insecticide applications to control the tarnished plant bug. These insecticide applications include organophosphate, pyrethroids, and neonicotinoids, all of which are capable of honey bee mortality. The increase in number of applications over previous years is largely a result of increased insecticide resistance and lack of efficacy of currently registered insecticides. In order to control tarnished plant bug, producers have been forced to apply insecticides in combination cocktails, which in turn further limits insecticide availability for complete season control of the pest. Furthermore, application of many of these insecticides results in outbreaks of secondary pests which in turn must be controlled by insecticide application. Data reviewed by EPA indicates that sulfoxaflor provides superior efficacy to most of the currently registered alternatives for key pests in cotton production. The use of sulfoxaflor would result in fewer pesticide applications overall (see commenter #s 0062, 0308, and 0059).

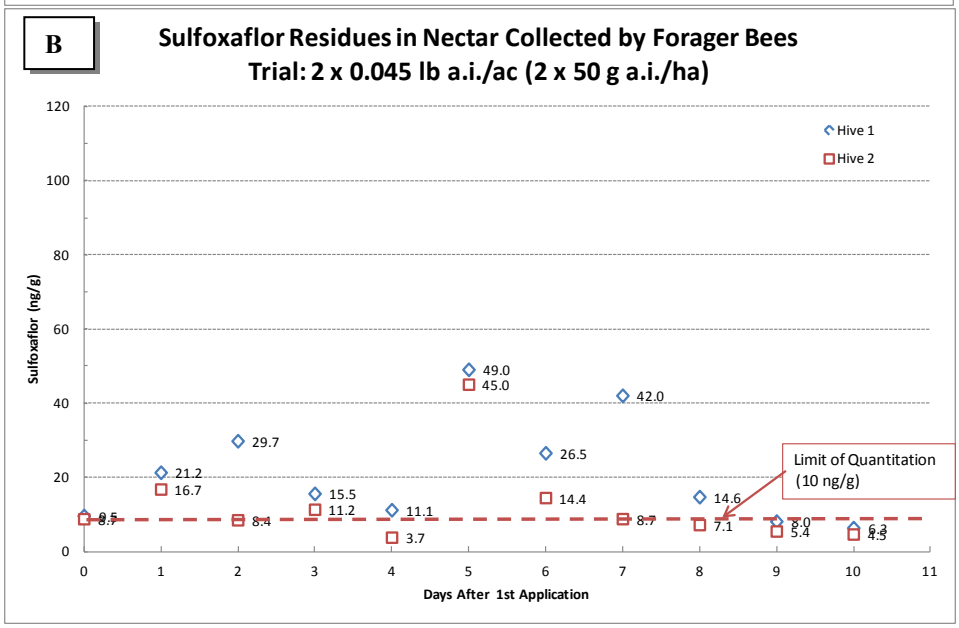
EPA agrees that effective weed control could be assumed to increase bee foraging directly on cotton. However, EPA has seen no data, nor did the commenter provided data other than anecdotal, which would either confirm or dispel this assumption. EPA is aware that Palmer amaranth has developed resistance to Roundup. However, EPA believes that a substantial stand of Palmer amaranth in a cotton field would trigger additional weed control measures by the farmer to ensure maximum yield and to prevent the weed from spreading to a wider area or greater density. Typically, farmers aim to control Palmer amaranth in the vegetative stage before flowering which would preclude its use by pollinators. In fields with high Palmer amaranth populations, farmers will often mow their fields to prevent the spread of this weed.

BEAD did note that cucurbits are one of the most dependent crops for honey bee pollination. This does seemingly concur with the comments identifying cucurbits as being responsible for some of the highest losses observed by beekeepers through acute poisonings cucurbits. Based on the Agency's Ecological Incident Information System (EIIS), no incidents have been reported for bees and cucurbits. Based on available information and the need to provide effective pest control in these crops, EPA has no basis to determine that the registration of sulfoxaflor would increase the number of acute poisonings over that of currently registered insecticides. Rather, as sulfoxaflor has greater efficacy than many of the currently registered insecticides, it is more likely that sulfoxaflor will be used in place of numerous applications of less effective insecticides and could reduce overall honey bee insecticide exposure.

EPA did not indicate that late evening sulfoxaflor would eliminate honey bee exposure but only indicated that "honey bee exposure to sulfoxaflor can be greatly reduced by limiting applications to late afternoon". While night time applications of sulfoxaflor may provide the greatest safety to honey bees in unique situations, this application timing is not realistic across all crops and regions. Due to regional differences in topography and infrastructure, night time application could potentially jeopardize worker safety, whether ground or aerial application. However, for those unique situations where insecticide applications can be safely applied at night (e.g. application by tractor with lights), this would still be an option based on best professional judgement.

Regarding the persistence of sulfoxaflor in plant tissue, available data from the cotton residue study indicate that residues in cotton nectar tend to decline steadily to levels approaching analytical detection limits within 3-4 days following application (see Figure 1A-1D below). Nectar is considered the dominant exposure route for forager bees based on their high nectar estimated consumption relative to pollen. The one exception occurred with the highest proposed application rate evaluated (2 x 0.134 lb ai/A; Figure 1D), in which one sample with 1 ppm sulfoxaflor occurred on day 8 (3 days following the second application). The Agency notes that the maximum proposed rate of sulfoxaflor (2 x 0.134 lb ai/A) was reduced to (0.086 lb ai/A) in an effort to reduce exposure to bees. It is further noted in the ecological risk assessment for sulfoxaflor that foliar dissipation half lives are generally 10 days or less and approximately half are 3 days or less.





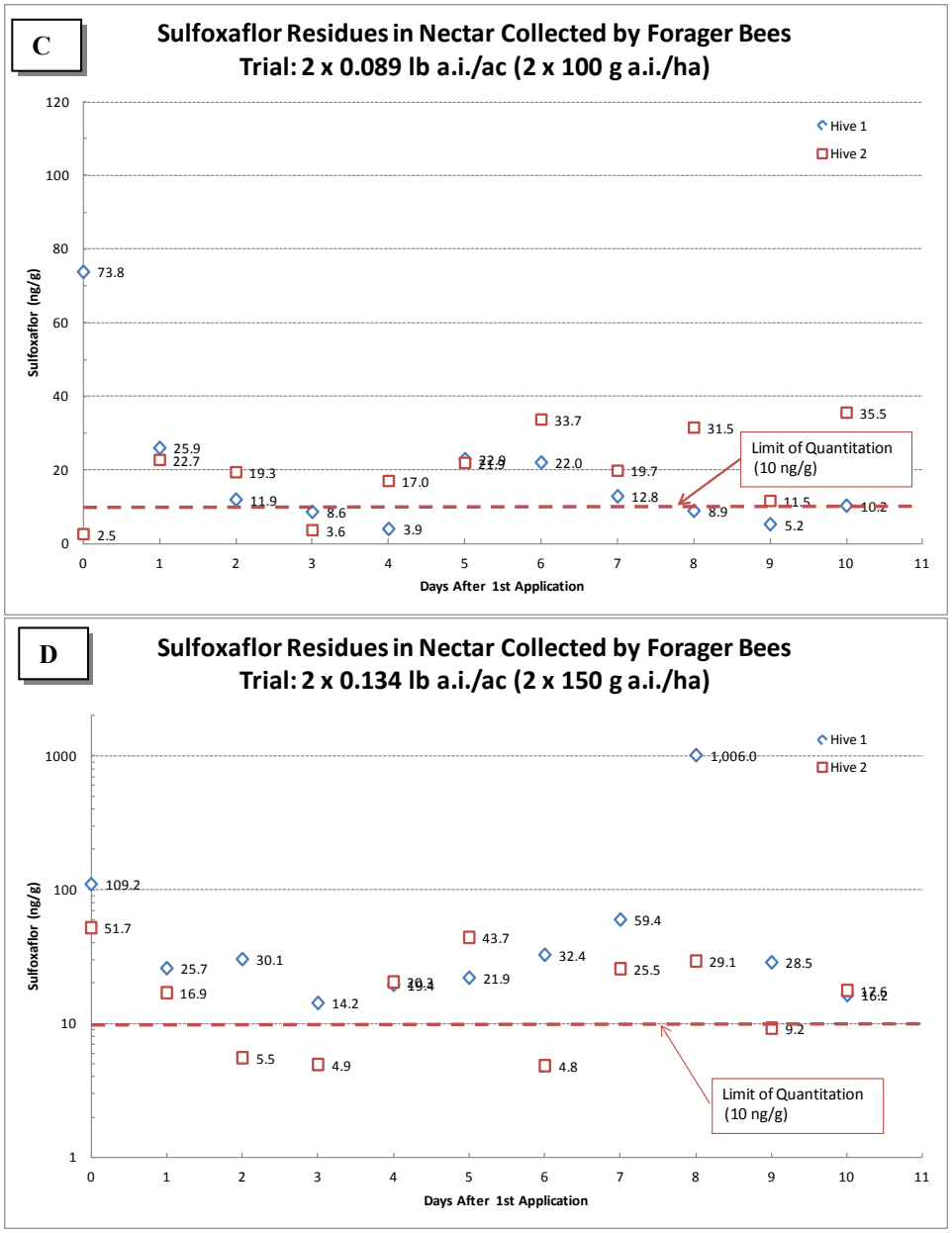


Figure 1. Profile of sulfoxaflor residues in cotton nectar following applications on Day 0 (A-D) and 5 (B-D); MRID 48755606

Regarding the assessment of honey bee exposure to multiple pesticide mixtures, evaluation of pesticide environmental mixtures to any taxa is considered beyond the scope of the EFED assessment because a myriad factors can affect exposure and effects of environmental mixtures which cannot be quantified based on the available data (USEPA, 2004). Those factors include identification of other possible co-contaminants and their concentrations, differences in the pattern and duration of exposure among contaminants, and the differential effects of other physical/chemical characteristics on the exposure and effects of chemical mixtures. Evaluation of factors that could influence additivity/synergism is beyond the scope of this assessment and the capabilities of the available data to allow for a quantitative evaluation of these factors. However, it is acknowledged that not considering mixtures could over- or under-estimate risks depending on the type of interaction and factors discussed above. The pollinator assessment, however, does evaluate the risk associated with sulfoxaflor formulated products (including

the inert ingredients such as surfactants that are used in formulating the active ingredient).

7) Impacts on commercial beekeepers

Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384): Commercial beekeepers from across the U.S. have been reporting honey bee kills that coincide with the planting of neonicotinoid-treated corn. Beekeepers, Beyond Pesticides, the Center for Food Safety, Pesticide Action Network, and others have already voiced concern to the agency over its continued lack of definitive action on the prevalence of bee-toxic pesticides in the environment. To that end, a petition requesting the agency to suspend the neonicotinoid, clothianidin, was submitted to the agency in 2012 and was supported by over one million signatures. Commercial beekeeping adds between $15 and $20 billion in economic value to agriculture each year. Without the yield increases made possible by commercial pollination services, food prices would rise, our farm sector would become less competitive globally, and the security and variety of our food supply would diminish.

Beekeepers across the U.S. are still losing hundreds of thousands of hives, and this is only expected to continue with spring plantings. The agency has not considered the synergistic impacts honey bees may experience with aggregate exposures to neonicotinoids and sulfoxaflor. Beekeepers have routinely identified multiple chemicals in their hives, most of which were encountered by their bees foraging on treated crops. Given that both sulfoxaflor and neonicotinoids share a similar mode of action, with sulfoxaflor being more potent in toxicity, would honey bees experience an enhanced, additive toxicological response? Would sub-lethal and chronic impacts to honey bee be more devastating? Even though sulfoxaflor is not currently registered for corn, it is to be used on other bee-attractive crops that are also currently treated with neonicotinoids. Would honey bee losses increase when using both neonicotinoids and sulfoxaflor? These questions have not been considered by the agency, but are being asked by concerned beekeepers.

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): The risk assessment also fails to take into account the impacts on the livelihoods of beekeepers, the national agricultural economy, and localized rural economies. Honey bees are the most economically valuable pollinator worldwide, and many high-value crops such as almonds and broccoli are entirely reliant upon pollination services by commercial beekeepers. Of the 100 crops that provide 90 percent of the world's food, over 70 are pollinated by bees. The value of crops pollinated by bees in the U.S. alone was estimated at $19.2 billion in 2010 – that figure has since grown.[47] This clearly multiplies the economic impacts of past EPA decisions on conditional registrations that have taken a major toll on beekeeper livelihoods, and counsels strongly against any more conditional registrations for additional neonicotinoids such as sulfoxaflor.

National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369): Consideration of the livelihood of the many small business owners who are commercial beekeepers is only a part of the economic analysis. In fact, according to the USDA, the pollination services provided by our bees are worth $15 billion in crop value in the U.S. alone.

EPA's response:

[47] Calderone NW. 2012. Insect Pollinated Crops, Insect Pollinators and US Agriculture: Trend Analysis of Aggregate Data for the Period 1992–2009. *PLoS ONE* 7(5): e37235.

The impact assessment was developed to evaluate benefits which would be associated with the registration of sulfoxaflor. Economics were not a component of this impact assessment. EPA appreciates the concerns expressed as to potential impact on beekeepers and the overall agricultural economy. EPA believes the additional labeling mitigation will reduce exposure to bees and therefore the potential for downstream effects would be minimized. Further, EPA would like to point out that while the commenters believe that there is a cascade effect for migratory beekeepers and pollinator dependent crops, there is also an impact on crops which do not rely on pollinators. While it is important to protect the pollinators to ensure the economic viability of pollinator dependent crops and commercial beekeeping, it is likewise important to ensure the economic viability of non-pollinator dependent crops by ensuring the availability of pesticidal tools to control pests which cause serious economic impact. The proposed label language as well as continued collaboration between beekeepers and growers, both by formal agreement and as common courtesy, should provide a balance and provide economic benefits to both.

Growers believe that without obtaining use of a chemical with a new mode of action such as sulfoxaflor, they may experience significant economic impacts and failure of their IPM programs. They state they would be forced to continue to rely on older chemistries, of which most pose risk to bees. Many growers familiar with field trials of sulfoxaflor said it is more effective on specific target pests and less injurious to beneficials. The use of sulfoxaflor can reduce the potential adverse effects from multiple applications of other pesticides. An IPM specialist from UC Riverside reported that registration of sulfoxaflor will reduce the number of applications of chlorpyrifos used to control citricola scale infesting citrus (comment 0161). If bees are foraging in or near citrus, this will lower their exposure to this organophosphate. Furthermore, a commenter from Louisiana State University AgCenter stated that the insecticides used for managing plant bugs in cotton rely heavily on organophosphates and neonicotinoids (see #2 above, comment 0059). He wrote that due to resistance issues they have seen a shift to the OP, acephate, synergized with pyrethroids, and neonicotinoid/pyrethroid mixtures. The commenter noted that unfortunately these insecticides have detrimental effects on arthropod natural enemies leading to outbreaks of secondary pests. Acephate is notorious for flaring spider mites, and pyrethroids are notorious for flaring spider mites and aphids. Thus, follow up applications of miticides or aphicides are often necessary following insecticide applications targeting plant bugs. Reducing the number of applications of insecticides would lessen the exposure of bees to these products.

The Agency conducted an extensive analysis of sulfoxaflor, encompassing all aspects of the pesticide, and focusing exhaustively on the pesticide's potential effects on animals, plants, soil, and water. EPA believes its analysis with respect to sulfoxaflor was consistent with the requirements of FIFRA.

Regarding the assessment of honey bee exposure to multiple pesticide mixtures, evaluation of pesticide environmental mixtures is considered beyond the scope of the ecological assessment for any taxa because a myriad factors can affect exposure and effects of environmental mixtures which cannot be quantified based on the available data (USEPA, 2004[48]).Those factors include identification of other possible co-contaminants and their concentrations, differences in the pattern and duration of exposure among contaminants, and the differential effects of other physical/chemical characteristics on the exposure and effects of chemical mixtures. Evaluation of factors that could influence additivity/synergism is beyond the scope of this assessment and the capabilities of the available data to allow for a quantitative evaluation of these factors. However, it is acknowledged that not considering mixtures could over- or under-estimate risks depending on the type of interaction and factors discussed above. The pollinator assessment, however, does evaluate the risk associated with sulfoxaflor formulated products (including

[48] USEPA. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency: Endangered and Threatened Species Effects Determinations. Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs, Washington, D.C. January 23.

the inert ingredients such as surfactants that are used in formulating the active ingredient).

8) Commercial beekeeping as a migratory operation

> **National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369):** The largest single fact that BEAD did not account for is that the bees that may be exposed to sulfoxaflor in cotton, tomato, citrus and cucurbit fields are the same bees that are absolutely critical for pollinating almonds, cherries, apples, pears, cranberries, blueberries, and more. It is almond pollination season right now, and there is a serious shortage of hives to fill the need for pollination services. The killing of bees by sulfoxaflor applications to cotton, cucurbits, and other fruits and vegetables may not affect the value of those crops, but it will affect both the livelihood of commercial beekeepers and the pollination services we provide to many other high-value crops. As the RaboBank report describes, the loss of commercial pollination services would result in substantial economic losses to agriculture as a whole.

EPA's response:

EPA acknowledges that bees may potentially be exposed to sulfoxaflor in numerous crops. However, EPA also acknowledges that sulfoxaflor is but one of many insecticides to which bees would potentially be exposed across the complex of crops mentioned in the comments. Exposure to multiple insecticides and/or multiple exposures to a single insecticide is inherent for mobile bee populations as hives are relocated throughout the country. Furthermore, and most importantly, EPA must point out that use of the other insecticides also has the potential for bee mortality. EPA is not aware of any information that would indicate that honey bee losses as a result of exposure to sulfoxaflor would exceed or be any different than those currently experienced with currently registered insecticides. EPA also believes the additional labeling mitigation will reduce exposure to bees and therefore the potential for downstream effects would be minimized. Furthermore, reliance on the most effective insecticides, such as sulfoxaflor, has the potential to increase levels of pest control and ultimately serve to reduce overall number of insecticide applications, as dictated by economic threshold levels of IPM programs, and therefore honey bee exposure.

Whether sulfoxaflor is or is not used on different crops, commercial honey bees will be exposed to a diverse array of pesticides and possibly other toxicants while they are transported around the country. Risk characterization integrates exposure and effects to provide an estimate of risk. Whether bees are managed as "for-hire" migratory colonies or are raised in stationary hives, they cannot be confined. A determination of quantifiable exposure from all sources to "free-roaming" organisms is extremely difficult.

9) Bee incident reporting system

> **Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384):** On a related note, EPA does not have an effective system in place for beekeepers to report bee incidents or have claims investigated. While much of the investigative actions belongs to states, beekeepers are frustrated that the federal agency has not played a major role in investigating incidents. Beekeepers believe that sulfoxaflor will compound their problems with bee losses, and find the agency irresponsible for proposing the registration of another chemical toxic to bees before sufficiently addressing the issues surrounding already registered chemicals that have an undeniable link to current bee losses. To that

end, EPA must carefully consider the impact that registering sulfoxaflor would have on the livelihoods of commercial beekeepers.

National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369): The proposed use of the conditional registration process begs the question of how EPA will determine whether sulfoxaflor can safely be used in agriculture. At present, there is no viable system for reporting and tracking pesticide poisonings of honey bees when they occur, making it impossible to document kills caused by problematic pesticides and restrict their use. It is critical that EPA develop and implement a valid mechanism for tracking poisoning events prior to the registration of sulfoxaflor and use this system to gather data on potential adverse effects.

EPA's response:

EPA receives incident data and it can be informative. EPA has a viable incident reporting system with a dedicated phone number and dedicated staff in attendance. The contact information has been published in bee journals and is listed on EPA's website. Historically, commercial beekeepers in particular have shown great reluctance to report incidents. State Lead Agencies and EPA have been told that beekeepers do not wish to offend growers who either hire their pollination services, or allow them on their land. However, EPA has reached out continuously, both on an individual basis, and publicly (such as at the 2013 North American Beekeeping Conference) to urge beekeepers to report incidents. Under FIFRA section 6(a)(2), pesticide registrants must submit factual information regarding unreasonable adverse effects on the environment. For example, Bayer submitted an incident report on the 2008 beekill incident in Germany and an independent investigation by Bayer of two beekill incidents in the Midwest in 2012. Both provided useful information on residues (or lack thereof) that were later corroborated by the state lead agencies. Further, Syngenta has provided incident reports where adverse effects have been detected in on-going studies underway in the European Union. These reports have alerted EPA to effects well before the study was completed and are used to inform risk assessments.

EPA has received no reports on any sulfoxaflor-related incidents from the 2012 use under section 18 authorizations. The state lead agencies informed EPA that they were not asked to conduct any investigations and they received no reports of adverse incidents.

10) Concern for birds

Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384): Sulfoxaflor raises concerns for bird populations as well. In a major scientific assessment that will soon be released by American Bird Conservancy, toxicologist Pierre Mineau reviews the effects of neonicotinoid insecticides on avian species and the aquatic systems on which they depend. The report raises red flags for birds that may apply to sulfoxaflor as well. EPA needs to proceed with caution.

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): The environmental persistence of the sulfoxaflor degradates and their neonicotinoid-like mode of action raise health and environmental concerns that go well beyond invertebrates. EPA identifies slight acute toxicity risks to birds, but states that sulfoxaflor is "practically nontoxic" on a sub-acute dietary basis. However, the passerine study on zebra finches was incomplete, and the acute oral LD50 could not be determined.[49] This is an area of uncertainty in the avian acute risk estimation that should be addressed with a second study.[50] Data is also lacking on effects from consumption of contaminated drinking water for all species, and EPA says that "sulfoxaflor exposure through drinking water alone has the

[49] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 68.
[50] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 90.

potential to be a relevant acute or chronic exposure route of concern for mammals or birds."[51] EPA also says that "additional refinements are needed to determine if actual risks result from this [drinking water] exposure pathway," but these refinements were not conducted.[52] This clearly shows a route of exposure and area of concern that is not adequately assessed by the EPA's RA that poses significant detrimental impacts to non-target species. In the case of imidacloprid, numerous recent studies have indicated surface water contamination exceeding EPA–recognized safe levels. The persistence of sulfoxaflor's metabolites in aquatic environments raises concerns similar to those posed by imidacloprid and other neonicotinoids. There are a number of concerns about the effects of neonicotinoids on avian species and the aquatic systems on which they depend that are only now being explored, and sulfoxaflor may pose similar threats.[53] Sulfoxaflor should not be approved without complete acute, subacute, and reproductive toxicity information on avian species, including completion of the passerine study.

EPA's response:

The lack of an LD_{50} in the avian passerine study with zebra finch occurred because birds regurgitated the dose at higher concentrations. Therefore, this study was unable to determine the extent to which birds that displayed this regurgitation behavior were exposed to sulfoxaflor. Passerine species tend to be much more prone to regurgitation of oral doses compared to Galliformes (quail) and Anseriformes (mallard duck). To account for this uncertainty, EPA made a conservative assumption in calculating its risk quotients (RQ) by using the highest tested dose which did not result in significant regurgitation as the denominator (80 mg/kg bw). The actual LD_{50} is expected to be greater than 80 mg/kg bw because no mortality occurred at this dose. Because the acute RQ for small (20g) birds consuming short grass is 0.70 based on the highest predicted EEC, only a slight increase in the LD_{50} (to approximately 100 mg/kg bw) would result in an acute RQ below the non-listed species LOC (0.5). Risk quotients for all other dietary items are all below the acute risk to non-listed species LOC of 0.5. Furthermore, it is apparent that the dietary concentration associated with an acute RQ of 0.5 (38 ppm on short grass) is exceeded for only 6 days out of the year based on T-REX modeling. Therefore, given conservative assumptions used in the passerine risk assessment and the likelihood that an additional study would lead to a finding of lower risk (not greater risk), the need for an additional study was not considered necessary.

Regarding the screening level assessment for drinking water exposure to wildlife using the SIP model, it should be understood that this assessment is only able to eliminate drinking water exposure as a potential exposure route of concern for concern and is not intended for identifying whether drinking water is actually a risk concern Specifically, the SIP model relies on highly conservative (upper bound) exposure assumptions including: 1) the concentration in the bird and mammal's drinking water is equivalent to the chemical's limit of solubility in water, and 2) 100% of the drinking water consumed by birds and mammals is contaminated at this level. Therefore, if based on these highly conservative estimates, the upper bound estimate of drinking water exposure is below the acute and chronic levels of concern, then it is concluded that that exposure through drinking water is not a concern. However, if the upper bound estimate of drinking water exposure exceed the levels of concern, then additional refinements are necessary in order to conclude whether there actually is a risk concern. For sulfoxaflor, if one assumes exposure via drinking water exposure pathway based on the aforementioned conservative assumptions, EPA cannot conclusively discount drinking water as a potentially relevant exposure pathway. This, however, does not indicate that drinking water is a risk concern. Additional refinements of the wildlife

[51] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 109.
[52] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 20.
[53] See forthcoming report from the American Bird Conservancy and toxicologist Pierre Mineau for more details.

drinking water exposure assessment are required before risk conclusions can be made. Currently, EPA does not have approved models for refining risk estimates to wildlife via drinking water. However, such approaches are in development and should be available for refining such screening level assessments in the future.

11) Concern for aquatic ecosystems

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): Aquatic ecosystems and the species that depend on them also face risks from systemic pesticides including sulfoxaflor. Surface water contamination resulting from the use of sulfoxaflor is expected to occur mainly from drift, rather than run-off. Plant residues that are left after crops are harvested are another potential route for surface water contamination. Drifted sulfoxaflor that reaches aquatic systems will likely persist, while that reaching soil systems is expected to break down quickly.[54] However, this assumption does not account for the major soil degradate, X-474, which is mobile and can run-off following sulfoxaflor application into surface waters. EPA states that "both surface and ground water contamination is expected from these three degradates following leaching drift/run-off events," clearly identifying a potential route of exposure for aquatic systems.[55] The RA does not assess the impact of the major degradate X-474 on aquatic environments, which should be remedied before sulfoxaflor is considered for registration.

While the acute toxicity to most aquatic species (flora and fauna) was determined to be fairly low, sulfoxaflor is highly acutely toxic to saltwater invertebrates.[56] This poses concerns for coastal uses of sulfoxaflor, but there is no apparent proposed mitigation through labeling or otherwise. Without mitigation and further exploration of sulfoxaflor's, and its degradates', toxicity to saltwater invertebrates, the use of sulfoxaflor in coastal areas presents a serious threat to estuarine and marine ecosystems.

Chronic toxicity of sulfoxaflor to aquatic species is examined, but the possibility for contamination of surface waters above the levels of concern is not addressed. In a key recent paper, Starner and Goh (2012) document that a significant portion of sampled surface waters were contaminated with imidacloprid above EPA-allowed levels for chronic invertebrate exposure across diverse agricultural landscapes in California.[57] Several other studies by the U.S. Geological Survey have found comparable aquatic contamination from the systemic neonicotinoids, which are similar in action to sulfoxaflor, in other environmental contexts.[58] The aquatic persistence of sulfoxaflor and its degradates, especially in anaerobic conditions, suggests that there may be similar levels of sulfoxaflor detected in waterways should it be registered. However, the proposed RA framework does not mention these water contamination studies nor does it quantify the risks to other species from comparable sulfoxaflor water contamination. The fact this environmental contamination by a major neonicotinoid exists now in California and elsewhere is indicative of agency failure to prevent undue consequences in its past risk assessments. The sulfoxaflor RA must be revised to correct this omission, or similar water contamination from sulfoxaflor is likely to impact aquatic ecosystems.

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[54] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.

[55] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.

[56] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.

[57] Starner K and Goh KS. 2012. Detections of the Neonicotinoid Insecticide Imidacloprid in Surface Waters of Three Agricultural Regions in California, USA, 2010-2011. *Bull Environ Contam Toxicol.* 88(3):316-21.

[58] Hladik ML and Calhoun DL. 2012. Analysis of the Herbicide Diuron, Three Diuron Degradates, and Six Neonicotinoid Insecticides in Water – Method Details and Application to Two Georgia Streams. USGS Scientific Investigations Report 2012-5206.; Smith KP. 2011. Surface-Water, Water-Quality, and Meteorological Data for the Cambridge, Massachusetts, Drinking-Water Source Area, Water Years 2007-08. USGS Open-File Report 2011-1077.

EPA's response:

Although sulfoxaflor is classified as 'highly acutely toxic' to saltwater invertebrates based on its 96-h LC_{50} of 0.64 mg ai/L, acute and chronic risk quotients for saltwater invertebrates are well below levels of concern (see Table 32 of the ecological risk assessment). It is noted that the units of the EEC should be expressed as ug ai/L in this table. Therefore, risks to saltwater invertebrates are not anticipated based on this risk assessment. As explained in the response to issue # 3, EPA believes the X-474 degradate should not be part of the residues of concern for ecological risk assessment of sulfoxaflor.

12) Non-*Apis* bees, other beneficial insects, and endangered species

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): The risk assessment's cursory treatment of the risks of sulfoxaflor to the ~4,000 species of native North American bees is unconvincing, a major failure given the severe declines many of these critical species are facing.[59] These bees lack the carefully-bred adaptability and resilient social structures of *Apis mellifera* and many have entirely different life cycles and vulnerabilities. Native species are at a far higher risk from pesticide toxicity than managed colonies of *A. mellifera*. The RA only mentions *Bombus* species in passing, and does not address other native pollinators. Acute oral toxicity to bumblebees is high, although the acute contact toxicity is lower than for honey bees. The oral toxicity of the formulated product is much higher for bumblebees than for honey bees, and toxicity for important native bee species is entirely unknown at this point. These unidentified additional effects on beneficial insect species should further dissuade EPA from registering sulfoxaflor prior to conducting comprehensive pollinator risk assessments.

There are numerous other beneficial insects and other invertebrates that are severely impacted by prophylactic applications of various commercial insecticides. EPA's knowledge of the impacts on these species is far more limited than its knowledge of the impacts on honey bees. Massive data gaps exist for beneficial non-bee insects such as butterflies, ladybugs and lacewings, dragonflies, hoverflies, and others, which are not addressed by the RA.

This section of the sulfoxaflor RA needs dramatic bolstering. If EPA proceeds with the current RA framework it appears likely that beneficial native insects, including rare and endangered species, will face continuing jeopardy. Given that many of these native species have small, localized native ranges, the assessment process should consider the need to restrict or limit the use of sufloxaflor in those locations, a consideration lacking in the document. Otherwise, exposure routes such as foliar spraying could effectively eliminate large portions of remaining populations of native bees and other beneficial insects. Overall, the applicant data submitted to EPA on *Apis* and non-*Apis* bees and other beneficial invertebrates is inadequate and fails to constitute an adequate effects analysis for Federally-listed threatened and endangered species as required by Section 7(a)(2) of the Endangered Species Act. This violates that Act and must be remedied.

EPA's response:

EPA acknowledges that compared to *Apis mellifera*, toxicity data for non-*Apis* bees is in general, much more limited. This is due in large part to the lack of standard toxicity testing protocols and limitations in

[59] See, for example, Evans E, et al. 2009. Status Review of Three Formerly Common Species of Bumble Bee in the Subgenus *Bombus*, Xerces Society. Available at: www.xerces.org/wp-content/uploads/2009/03/xerces_2008_bombus_status_review.pdf .

availability of *non-Apis* species that are appropriate for regulatory application. However, as described in EPA's recent Proposed for Pollinator Risk Assessment[60], pollen and nectar consumption rates for *A. mellifera* appear protective of those for several non-*Apis* species for which consumption information is known (*e.g.,* European mason bees, alfalfa leaf-cutter bees, bumble bees). Although other exposure routes (*e.g.,* soil) may be more important to certain non-*Apis* bees (*e.g.,* ground nesting bees), the properties of sulfoxaflor and its application method are not expected to result in ecologically significant levels in soil. Specifically, sulfoxaflor is applied as a foliar treatment rather than a soil application. Furthermore, any amount of sulfoxaflor that reaches the soil is expected to rapidly degrade to the X-474 degradate which is practically non-toxic to bees. Regarding pesticide toxicity, EPA is not aware of information that suggests non-*Apis* bees would tend to be more or less sensitive to pesticides compared to *A. mellifera*. Therefore, until toxicity protocols are established and validated for regulatory application with non-*Apis* bees, EPA will continue to rely on risk assessment of *Apis* as a surrogate organism for bees in general. This approach is consistent with the Agency's use of the surrogate species methods for pesticide ecological risk assessment for all other taxa.

EPA appreciates the comment raised regarding endangered species. Based on the risk profile for the proposed uses of sulfoxaflor, the Agency has determined that such registration would result in a "No Effect" determination for listed freshwater and estuarine/marine fish, aquatic invertebrates, and aquatic plants in relation to direct effects on these listed taxa. Similarly, the Agency makes a "No Effect" determination for direct effects on listed terrestrial plants. These 'No Effect' determinations are based on the lack of exceedence of the Agency's acute and chronic risk levels of concern (LOC) for listed species in these taxonomic groups. For listed birds, mammals and terrestrial invertebrates, the acute or chronic listed species LOC values were exceeded for one or more proposed uses. Therefore, the Agency cannot make a determination at this time until the temporal and spatial co-occurrence of listed species with sulfoxaflor use patterns is identified and evaluated.

EPA is currently developing tools that are expected to further refine the assessment and are designed to support effects determinations for individual federally listed species and their designated critical habitats (where applicable). Scientific information obtained from the U.S. Fish & Wildlife Service (USFWS), the National Marine Fisheries Service (NMFS), and other reliable sources is being collated by EPA to address all currently listed species. The information will be stored in an Office of Pesticide Programs Pesticide Registration Information SysteM (PRISM) knowledgebase. The listed species knowledgebase will consist of an information repository that houses biological and behavioral information relevant to individual species (*e.g.*, habitat, diet, and life history, including specific temporal and spatial associations) and a document repository that contains supporting documents (*e.g.*, USFWS recovery plans) and electronic information (*e.g.*, GIS data files). For terrestrial taxa, the biological information relevant to risk quotient (RQ) calculations (*e.g.*, diet and body weight) will be used to parameterize exposure estimates to derive species-specific RQs using a method consistent with currently used methods in the T-REX and T-HERPS models.

Refinements may also include more detailed analyses of the registered uses and their use patterns that result in LOC exceedances for federally listed species in the screening-level assessment. The analyses may include more information on where, when, and how sulfoxaflor is used on selected crops for which LOCs are exceeded. Actual usage data (when available) and national land-cover datasets that indicate potential use sites (*e.g.*, national land cover dataset (NLCD), crop data layer (CDL)) may be used to support a more refined analysis of where sulfoxaflor is reasonably expected to be used. Similarly, refinements for the timing of applications and how sulfoxaflor is used may be based on the analysis of additional usage data, beyond what were available at the time of the screening-level assessment, and a more in-depth exploration of agronomic practices.

[60] available at: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0543-0004

In addition, a committee of the National Research Council (NRC) has been tasked with providing advice on ecological risk assessment tools and scientific approaches under ESA and FIFRA (Project Identification Number DELS-BEST-11-01). The committee has been asked to review the use of "best available data"; methods for evaluating sublethal, indirect, and cumulative effects; the state of the science regarding assessment of mixtures and pesticide inert ingredients; the development, application, and interpretation of results from predictive models; uncertainty factors; and what constitutes authoritative geospatial and temporal information for the assessment of individual species and habitat effects. The Agency recently received the NRC report on April 30, 2013, which is currently being reviewed.

The refinements based on individual species data; additional, detailed usage information, when available; and further recommendations from the NRC report are expected to help to more accurately identify potential areas of effect and to better inform effects and habitat determinations for listed species and any designated critical habitats. For example, if sulfoxaflor is used when a particular species of concern is not present (*e.g.*, it is migratory) or is not co-located in space, then risk of potential direct effects to the species may often be precluded. If LOCs are still exceeded after conducting the refined analyses, further analyses of the potential spatial and temporal co-occurrence of listed species of concern (and any designated critical habitat) may be conducted. The extent of possible refinement in the analyses of spatial/temporal co-occurrence will largely depend on the scale and quality of the available sub-county level use site (*e.g.*, NLCD, CDL) and species location data.

It is further noted that sulfoxaflor is a replacement for a number of insecticide classes (organophosphates, carbamates, pyrethroids and some neonicotinoids) that present greater risks to a wide-range of non-target species than sulfoxaflor; registration of sulfoxaflor should therefore serve to reduce overall risks to such species, including listed species, when users substitute this product for the majority of the available registered alternatives.

13) Mammalian toxicity, the FQPA safety factor, and the interspecies uncertainty factor

> **Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384):** Sulfoxaflor is classified as "suggestive evidence of carcinogenic potential" based on the incidence of tumors and carcinomas in mice and rats. In carcinogenicity studies, increased incidence of interstitial cell tumors was observed but EPA does not consider these to be treatment related due to a lack of dose-response. Tremors, convulsions, hind limb splaying etc were also observed, and EPA also questions the cause of these. Significant hepatocellular adenomas were observed at high doses of sulfoxaflor in rats. Carcinomas and hepatocellular adenomas were seen in mice. Perputial gland tumors, while observed, were difficult to relate to treatment, leading to the agency's classification of "suggestive evidence of carcinogenic potential." Developmental abnormalities (skeletal, neonatal death) were observed in rats, liver weight and enzyme changes, hypertrophy, tumors were also observed in sub-chronic and chronic studies.
>
> Despite this and the need for an outstanding study, EPA believes that data are "sufficient to support reducing the interspecies uncertainty factor to 3X for the developmental effects," even though many of the studies were lacking. One industry study observed that sulfoxaflor affected the fetal, not adult, rat muscle nAChR and that prolonged exposure caused sustained striated muscle contracture resulting in concomitant reduction in muscle responsiveness to physiological nerve stimulation. According to the study, fetal effects were inducible with as little as one day of exposure at the end of gestation, but were rapidly reversible after birth.[61] While sulfoxaflor does have significant measurable neurotoxic

[61] Rasoulpour RJ, Ellis-Hutchings RG, Terry C, et al. 2012. A novel mode-of-action mediated by the fetal muscle nicotinic acetylcholine receptor

activity in mammalian system (mice and rats), it has been concluded that these effects are not relevant to humans. A search of the literature found no other studies evaluating the effect of sulfoxaflor on mammalian systems and so, much is still unknown about this chemical's potency in humans. However, as a chemical whose mode of action involves selective activity at nAChRs like neonicotinoids, sulfoxaflor effects must not be dismissed so easily. For neonicotinoids, excitatory effects on mammalian nAChRs (increasing anxiety behavior) at concentrations greater than 1 μM have been documented, with speculation that this class of chemicals may adversely affect human health, especially the developing brain.[62] [63] One study out of Duke University Medical Center found that gestational exposure to a single, nonlethal dose of imidacloprid produces significant neurobehavioral deficits and an increased expression of pathological alterations in several brain regions of the offspring of Sprague-Dawley rats, at an age that corresponds to early human adolescence. The authors conclude that these changes may have long-term adverse health effects in the offspring.[64]

Even though there are no residential uses at this time, the Food Quality Protection Act (FQPA) safety factor should not be reduced from 10X to 1X, nor should the interspecies uncertainty factor be reduced to 3X since much is still unknown about developmental neurotoxicity. Given the mode of action similarities between sulfoxaflor and neonicotinoids, the higher potency of sulfoxaflor, and its carcinogenic potential, an FQPA safety factor of 10X should be retained.

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): Sulfoxaflor's potential mammalian and human toxicity has not been adequately evaluated. In carcinogenicity studies, increased incidence of interstitial cell tumors were observed but EPA does not consider these to be treatment related due to a lack of dose-response. Tremors, convulsions, hind limb splaying, etc. were also observed, and EPA is unsure about the cause of these. Significant hepatocellular adenomas were observed at high doses of sulfoxaflor in rats. Carcinomas and hepatocellular adenomas were seen in mice. Perputial gland tumors, while observed, were difficult to relate to treatment, leading to the agency's classification of sulfoxaflor as having "suggestive evidence of carcinogenic potential." Developmental abnormalities (skeletal, neonatal death) were observed in rats, liver weight and enzyme changes, hypertrophy, tumors were also observed in sub-chronic and chronic studies.

Despite these demonstrated effects, EPA believes that data are sufficient to support reducing the interspecies uncertainty factor to 3X for the developmental effects, even though many of the studies were lacking. One industry study observed that sulfoxaflor affected the fetal, not adult, rat muscle nAChR and that prolonged exposure causes sustained striated muscle contracture resulting in concomitant reduction in muscle responsiveness to physiological nerve stimulation. According to the study, fetal effects were inducible with as little as one day of exposure at the end of gestation, but were rapidly reversible after birth.[65] While sulfoxaflor does have significant measurable neurotoxic activity in mammalian systems (mice and rats), it has been concluded that these effects are not relevant to humans. A search of the literature found no other studies evaluating the effect of sulfoxaflor on mammalian systems and so, much is still unknown about this chemical's potency in humans.

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resulting in developmental toxicity in rats. *Toxicol Sci.* 127(2):522-34.

[62] Kimura-Kuroda J, Komuta Y, Kuroda Y, Hayashi M, Kawano H. 2012. Nicotine-Like Effects of the Neonicotinoid Insecticides Acetamiprid and Imidacloprid on Cerebellar Neurons from Neonatal Rats. *PLoS ONE* 7(2): e32432. doi:10.1371/journal.pone.0032432

[63] Rodrigues KJ, Santana MB, Do Nascimento JL, et al. 2010. Behavioral and biochemical effects of neonicotinoid thiamethoxam on the cholinergic system in rats. *Ecotoxicol Environ Saf.* 73(1):101-7.

[64] Abou-Donia MB, Goldstein LB, et al. 2008. Imidacloprid induces neurobehavioral deficits and increases expression of glial fibrillary acidic protein in the motor cortex and hippocampus in offspring rats following in utero exposure. *J Toxicol Environ Health A*. 71(2):119-30.

[65] Rasoulpour RJ, Ellis-Hutchings RG, Terry C, et al. 2012. A novel mode-of-action mediated by the fetal muscle nicotinic acetylcholine receptor resulting in developmental toxicity in rats. *Toxicol Sci.* 127(2):522-34.

However, as a chemical whose mode of action involves selective activity at nAChRs like neonicotinoids, sulfoxaflor effects must not be dismissed so easily. For neonicotinoids, excitatory effects on mammalian nAChRs (increasing anxiety behavior) at concentrations greater than 1 μM have been documented, with speculation that this class of chemicals may adversely affect human health, especially the developing brain.[66] [67] One study conducted at Duke University Medical Center found that gestational exposure to a single, nonlethal dose of imidacloprid produces significant neurobehavioral deficits and an increased expression of pathological alterations in several brain regions of the offspring of Sprague-Dawley rats, at an age that corresponds to early human adolescence. The authors conclude that these changes may have long-term adverse health effects in the offspring.[68] Results such as these should prompt a closer review of sulfoxaflor's potential impacts to mammals.

Even though there are no residential uses at this time, the Food Quality Protection Act (FQPA) safety factor should not be reduced from 10X to 1X, nor should the interspecies uncertainty factor be reduced to 3X since much is still unknown about developmental neurotoxicity susceptibility. Given the mode of action similarities between sulfoxaflor and neonicotinoids, the higher potency of sulfoxaflor, and its carcinogenic potential, an FQPA safety factor of 10X should be retained. Much is still unknown about sulfoxaflor's mammalian toxicity, so EPA should evaluate sulfoxaflor with conservative safety factors.

EPA's response:

The comments express concern about the evaluation that EPA has made regarding the carcinogenicity and developmental effects of sulfoxaflor. The response, below, is aimed at better explaining the Agency's decisions, which were laid out in the human health risk assessment. EPA has evaluated these areas of toxicity separately; therefore, the response is divided into two parts.

Carcinogenicity: The carcinogenic potential of sulfoxaflor was evaluated by the Agency's Cancer Assessment Review Committee (CARC). This group consists of expert toxicologists from across the Agency. In addition to reviewing the work of the lead toxicologist for the risk assessment, the group ensures that determinations of carcinogenic potential adhere to the 2005 Guidelines for Carcinogen Risk Assessment. In the case of sulfoxaflor, the evaluation included guideline studies of carcinogenicity in male and female rats and mice as well as non-guideline studies designed to specifically elucidate the mode of carcinogenic action of the compound. The guideline studies showed increases in liver tumors and preputial gland carcinomas. The data indicated that the liver tumors were treatment related and that the preputial gland carcinomas may have been treatment related. Leydig cell tumors were also observed in these studies; however, their incidence rate was not significantly different from historical control values. Therefore, the Leydig cell tumors were not considered to be treatment related.

EPA has not concluded that there is no cancer risk from exposure to sulfoxaflor. Rather, the Agency determined, in accordance with the guidelines, that (1) there is "Suggestive Evidence of Carcinogenic Potential" for sulfoxaflor, (2) a non-linear assessment of cancer risk from exposure to sulfoxaflor is appropriate and (3) that a chronic assessment will adequately account for cancer as well as non-cancer

[66] Kimura-Kuroda J, Komuta Y, Kuroda Y, Hayashi M, Kawano H. 2012. Nicotine-Like Effects of the Neonicotinoid Insecticides Acetamiprid and Imidacloprid on Cerebellar Neurons from Neonatal Rats. *PLoS ONE* 7(2): e32432.

[67] Rodrigues KJ, Santana MB, Do Nascimento JL, et al. 2010. Behavioral and biochemical effects of neonicotinoid thiamethoxam on the cholinergic system in rats. *Ecotoxicol Environ Saf*. 73(1):101-7.

[68] Abou-Donia MB, Goldstein LB, et al. 2008. Imidacloprid induces neurobehavioral deficits and increases expression of glial fibrillary acidic protein in the motor cortex and hippocampus in offspring rats following in utero exposure. *J Toxicol Environ Health A*. 71(2):119-30.

toxicity. In light of the comments regarding the reduction of the interspecies uncertainty factor to 3X, the Agency notes that the reduction is only for one risk assessment scenario (i.e., acute dietary) and that the interspecies factor is retained at 10X when assessing chronic risk.

Developmental Effects and the FQPA Safety Factor; Reduction of the Interspecies Factor: The Agency is required to apply the additional 10X FQPA Safety Factor to account for potential increased susceptibility of infants and children to the adverse effects of exposure to pesticides. The factor is assumed to be 10X unless, based on reliable data, the Agency can determine that another safety factor is appropriate. When considering reduction of the FQPA Safety Factor, the Agency examines the completeness of the toxicological database, any observed quantitative or qualitative susceptibility observed in that database, the doses and endpoints selected for risk assessment, and the extent to which exposure estimates may underestimate actual exposures. If, after taking those factors into account, there is any residual uncertainty with regard to pre- and/or post-natal susceptibility, then the FQPA Safety Factor is retained at 10X.

In the case of sulfoxaflor, reproduction studies with rats showed developmental abnormalities at low doses. The studies show that the developmental effects could be attributable to a single, *in utero* exposure; therefore, the Agency selected those effects as the endpoint of concern when assessing acute exposure to women of child-bearing age (females 13-49 years of age). The 10X FQPA Safety Factor was reduced to 1X given that:

- The doses and endpoints selected for risk assessment purposes are based on sulfoxaflor's developmental effects observed in the susceptible population group,
- The sulfoxaflor database is complete, including numerous non-guideline mechanistic studies designed to elucidate the mode of action resulting in the observed developmental effects and,
- Exposure estimates are conservative and are not expected to underestimate actual exposure estimates.

When considering these factors in concert, the agency has concluded that there are no residual uncertainties with regard to susceptibility.

As discussed in the human health risk assessment, the mechanistic studies provided evidence that the developmental effects were, in fact, due to a neurological mechanism – specifically, that activation of the nicotinic acetylcholine receptor (nAChR) by sulfoxaflor was causing prolonged muscle contraction in unborn rat pups. The prolonged contractions adversely affected the skeletal system and, in the most severe cases, resulted in death of newborn pups due to asphyxiation. These studies also demonstrated that activation of the nAChR by sulfoxaflor was highly specific to the fetal isoform of the receptor. The specificity of the receptor to activation by sulfoxaflor as well as the differences between rats and humans in the timing of the expression of the fetal and adult isoform types provide strong evidence that the developmental effects being used as the endpoint for risk assessment are not likely to be relevant to humans. Despite the evidence that the mode of action resulting in the developmental effects is not likely to be relevant to humans, out of an abundance of caution, the Agency chose to regulate on the developmental endpoint due to the severity of the effects.

The special mode of action studies provided support for reducing the interspecies factor for risk assessments based on the developmental effects. Specifically, the studies demonstrated significant pharmacodynamic differences (PD) between rats and humans, with respect to binding and activating the nicotinic receptor. The data demonstrate that sulfoxaflor does not elicit a response in the human nAChR at concentrations 500-fold higher than the concentrations eliciting a response in the uniquely susceptible fetal rat receptor. Since humans are clearly not more sensitive pharmacodynamically to sulfoxaflor compared to the rat, reduction of the UF for PD to 1X, which assumes an equal response between humans and rats, is conservative. The agency has, however, retained the 3X pharmacokinetic portion of the interspecies uncertainty to account for potential pharmacokinetic differences between rats and humans.

Thus, HED's retention of a 3X interspecies factor is both protective and conservative.

14) Sulfur allergies

> **J. Roberts' (private citizen) comment (Docket # EPA-HQ-OPP-2010-0889-0032)**: I am allergic to Sulfur and Iodine. I am hoping that this Sulfur based pesticide is not approved, because I'm sure that there are many people like me who would either be made terribly sick by eating these foods treated with Sulfur based pesticide, or would simply have to stop eating them unnecessarily. There is no provision for labeling foods that have been treated with one pesticide or another, so many people would be affected without the ability for them or their physician to understand why.

EPA's response:

Sulfoxaflor does contain a sulfur atom as part of its molecular backbone, and sulfur is also present in a number of metabolites and degradates. Studies available for sulfoxaflor adequately reflect the potential toxicity of the parent and any sulfur-containing metabolites; estimated risk from sulfoxaflor and its metabolites in food and water are well below OPP's level of concern.

15) Impacts on human immune systems and pregnant women

> **J. Watson's (private citizen) comment (Docket # EPA-HQ-OPP-2010-0889-0237)**: The EPA has proposed to register a new insecticide, Sulfoxaflor, which the agency has classified as "very highly toxic" to honey bees. The disappearance and killing of Honeybees has been linked to damaged Honeybee immune systems, which is possibly caused by these toxic insecticides. Not only is there a danger to the honeybees but Sulfoxaflor toxins entering the plant stem, leaves, blossoms, nectar, fruits and vegetables are also sold to consumers and served to families without the ability of the food preparer to wash or remove the pesticides. Therefore, in addition to Bees, Sulfoxaflor may affect the human immune systems, particularly pregnant mothers ingesting the pesticides contained in these plants and passing them on to their unborn children to result in weakened or damaged immune systems which may make them susceptible to diseases from cancer to autism. I propose that the EPA conduct research studies "independent" of those conducted by the pesticide companies to determine if Sulfoxaflor poses a danger to both Bees and humans eating these plants and what effect it has on unborn children whose mothers have eaten these pesticide laden plants. That until a proper and full research studies are performed that the EPA immediately ban the use of Sulfoxaflor.

EPA's response:

As part of its review, the Agency examines studies specifically designed to assess immune function. In addition, the Agency looks for evidence of immunotoxicity, such as effects on the thymus and spleen, in other toxicity studies. There is no indication in any of these studies that sulfoxaflor impacts the immune system of mammals, including humans. Regarding pregnant females, the Agency has reviewed developmental toxicity studies in the rat and rabbit, as well as a reproductive toxicity study and a developmental neurotoxicity study in the rat. These studies assess the impact on both the parental animals and the offspring and therefore endpoints resulting from these studies will be protective of developing offspring and the pregnant females. These studies include gavage and dietary studies, and would reflect dietary exposure to pregnant females. Furthermore, high-end inputs related to dietary exposure, such as use of residue data from field trials, conservatively modeled estimates of residues in drinking water, and an assumption that all of the crops for which registration was sought were, in fact, treated with sulfoxaflor, did not result in risks of concern. The studies submitted by pesticide companies

to the Agency for evaluation of sulfoxaflor were conducted in accordance with Good Laboratory Practice (GLP) guidelines and have been accepted by the US, Canada, and Australia. The GLP guidelines are intended to ensure the quality and integrity of data submitted to the Agency and the results of these studies are considered appropriate for use in human health risk assessment. EPA has determined that no additional studies are needed to address the concerns raised in this comment.

16) Impractical and/or unenforceable label statements

Beyond Pesticides' comment (Docket # EPA-HQ-OPP-2010-0889-0384): Sulfoxaflor's proposed label statements attempt to warn the user of the risks to bees. However, these labels seem to be unrealistic in the real world and unenforceable. Statements advising users to make applications before 7.00am or after 7.00pm ignore EPA's own data that the product is still highly toxic up to three days after application. While spraying before and after bees are active in fields may minimize direct contact exposures, residual exposures, at least up to three days, are still highly toxic and do not solve the problem of minimizing risks.

Other label statements that are currently in use include: "Do not apply during bloom"; "Do not apply three days prior to bloom…"; "Do not make more than one application...three days prior to bloom" etc. These have not been practical or enforceable. The agency is aware that label directions such as these are not adhered to in the real-world. Many beekeepers can attest to this. Addressing lack of compliance has been an area the agency has not sufficiently addressed throughout the years. These labels are also unenforceable. Moreover, instructions to minimize pesticide drift continue to be a challenge especially for aerial applications.

Meanwhile, EPA and state enforcement capabilities seem to be almost non-existent. Many states do not have the resources or manpower to enforce product labels, collect incident data, or conduct necessary inspections. Given the challenges that exist with product label compliance, and the declines in bee populations in the U.S., the agency must reconsider granting registration to a product with such high risks to bees without the proper safeguards in place.

National Pollinator Defense Fund's comment (Docket # EPA-HQ-OPP-2010-0889-0369): Protection of pollinators from sulfoxaflor poisonings requires that label restrictions be enforced, yet the discussions within the PPDC Pollinator Workgroup have made it clear that enforcement at the state level is dysfunctional in many states. Label statements are confusing and undefined, and the State Lead Agencies in charge of enforcement believe them to be unenforceable. The result is that readily preventable acute bee kills still happen with regularity and with impunity for those causing the kills. EPA can solve this problem by clarifying label language and ensuring that states require mandatory training in pollinator protection for applicators and require state regulators to take their enforcement mandate seriously by acting expeditiously to fully investigate each incident, document the incident in a traceable manner, file a comprehensive report of the incident with US EPA, and take corrective action to avert future poisoning incidents.

Thomas R. Smith's comment (Docket # EPA-HQ-OPP-2010-0889-0342): 5. The Environmental Section mandatory language as it pertains to pollinators for the Sulfoxaflor label will not be followed by applicators nor enforced by State Lead Enforcement Agencies. This is the current situation for existing pesticide labels. This fact has been reported by the beekeeping industry to EPA during the PPDC discussions and by past industry leaders for decades. This fact is also substantiated by State Lead Agencies stating in the PPDC work group session, on more than one occasion, that the current mandatory label language does not consist of "legal" terms. It is common knowledge that EPA has not defined the mandatory terms. It is also documented that the request for definitions has gone

unanswered for decades. State Lead Agencies have stated that the mandatory terms cannot be determined in the field therefore they not enforceable. In practice the Environmental Section is deemed as Advisory language in the eyes of applicators and State Lead Enforcement Agencies. There is no evidence that the Mandatory language for Sulfoxaflor would be followed based upon this evidence.

6. The vast majority of Sulfoxaflor applications will occur as other pesticide applications are presently occurring. In crops which are not dependent upon pollinators, the applications will begin at sunrise and end at sunset resulting in unacceptable damage to pollinators exposed to direct contact and highly contaminated pollen. Applications will occur in similar fashion for crops which require pollination when managed pollinators colonies are not present in the field under contract. Applicators will follow the Mandatory language when managed pollinator colonies are present in the field under contract. Sadly native pollinators will suffer when managed colonies are not present and under contract.

The Section 18 Permit utilized a beekeeper written notification as the risk mitigation measure to protect managed honey bee colonies. In reality this was a notice for beekeepers to move their colonies and place them where another farmer will have to protect them. Notification is not a mitigation measure. Notification programs are not acceptable to the commercial honey bee industry, as has been stated in the PPDC work group's records and the PPDC meetings. Moving colonies to facilitate pesticide applications is not a sustainable business or colony management model. Managed pollinators and the majority of native pollinators must reside near good soils with adequate rainfall or irrigation. The poor soils lacking adequate water will not sustain the pollinators or production agriculture. The two are forced to coexist. It will be of no value for EPA to include a notification requirement on the Sulfoxaflor label. The bees will not be moved. They will just be damaged.

The only possible recommendation I can provide is for EPA to include clear Advisory language which will define the Mandatory language intent. Including how long Sulfoxaflor will kill bees in the different crops in bloom if the Mandatory language is followed. Also provide the expected damage to pollinators if the Mandatory language is not followed and applications are made as I expect, from sunrise to sunset to blooming crops.

The proposed label language states application be completed before 7:00 hours AM and after 7:00 PM. My first question would be: Is these times Mandatory? Second question: Is the language adequate to dispel confusion concerning Daylight Savings Time? For the sake of example, I will assume the language is adequate to describe the sunrise/sunset tables published in the newspaper. Let's assume the median cotton belt latitude is Dallas, Texas. Also for this example, let's assume adequate natural light exists to safely operate all application equipment for 30 minutes before sunrise and 30 minutes after sunset. On July 1, 2013 in Dallas, Texas the sunrise occurs at 6:23 AM and sets at 8:39 PM. Providing for 30 minutes before and after sunrise and sunset the time for which adequate light will exist the label language would define applications times as:

5:23 to 7:00 AM = 1 hour 7 minutes
7:00 to 9:09 PM = 2 hours 9 minutes
Totaling 3 hours 16 minutes daily

My points of this example are:
1. Honey bees will absolutely be exposed to direct contact based their habits and the defined language application times.

2. It has been reported and documented in the PPDC workgroup session that the official position of the Aerial Applicators is that night applications are not safe. (This position does not reflect that aerial night applications have been practiced in many areas since the 1970's and are standard practice when bees are located in pollination fields .)
3. It has been voiced by the Cotton Council that ground application equipment also cannot safely be operated at night in the PPDC work group meetings.
4. The total daily defined application period of 3 hours 19 minutes will not be observed by applicators. The expectation of applicators to prepare for only 1 hour and 7 minutes in the morning and return for 2 hours 19 minutes in the late afternoon will be considered absurd!
5. EPA must be assume, based on this information, that applicators will apply Sulfoxaflor from first light to sunset. State Enforcement Agencies will be influenced by political pressure and allow applications to occur by deeming the label language "Advisory".
6. EPA can only conclude the pollinators will be directly exposed to and, severely damaged by, Sulfoxaflor applications.

Center for Food Safety's comment (Docket # EPA-HQ-OPP-2010-0889-0363): There are several areas where EPA suggests potential mitigation efforts for certain crops to reduce pollinator exposure (e.g., timing applications for late in the day for cucurbits), but these are only offered as voluntary applicator practices, not requirements. On the proposed label, application is required to avoid bloom periods for certain crops, but this is not adequate to protect pollinators from pre-bloom applications because of the systemic nature of sulfoxaflor. These mitigation efforts also do not reduce the likelihood of bees contacting sulfoxaflor via drift on to neighboring lands, and essentially ignore the higher exposure likelihood on the day of application. The systemic nature of sulfoxaflor and its major degradates means that these suggested mitigation measures will not be adequate to protect honey bees and other pollinators from exposures.

EPA's response:

EPA has proposed mitigation measures for sulfoxaflor which include lowering application rates and lengthening the interval between applications. These mitigation measures are mandatory and therefore enforceable. The label also includes the mandatory prohibition against application prior to bloom, during bloom and until after petal fall for a number of crops. These statements are mandatory and enforceable. Advisory statements regarding making applications in the early morning and late evening, and when the temperature is <55˚F, will inform growers of additional steps they can take to minimize exposure to foraging bees. Additionally, EPA agrees with commenter #0342 that notification is not a mitigation measure, however, the sulfoxaflor label will include a recommendation that beekeepers in the area be notified of planned applications so that beekeepers may be informed and communication and coordination between growers and beekeepers may be enhanced.

Commenters state that enforcement capabilities at the state and Federal level are nonexistent due to reduced resources and poor labeling. They also state that the Agency is aware that label directions are not adhered to. There is some degree of misuse in all commodities and instances where applicators have willfully ignored label restrictions or used unauthorized pesticides. In fact, EPA has taken enforcement action for misuse in numerous situations such as adulteration of crops (ex. misuse of zeta-cypermethrin on wheat in multiple states in 2001) and when spray drift has caused adverse effects (ex. clomazone damage to residential properties). EPA is aware that beekeepers themselves have resorted to the use of unregistered miticides and other compounds to combat Varroa mites and other hive pests. However, EPA believes that most growers and beekeepers apply pesticides according to the approved labeling. Furthermore, because bee kill incidents are unique, EPA is collaborating with states, with input from pollinator experts, in order to develop guidance to assist inspectors to better investigate alleged bee kill incidents.

Registration of sulfoxaflor is expected to replace multiple applications of older chemistries (ex. organophosphates, pyrethroids) and will displace applications of compounds in other neonicotinoid subgroups. Therefore, sulfoxaflor is not expected to present an additive risk scenario for pollinators. Additionally, as noted by the National Pollinator Defense Fund, the PPDC Pollinator Workgroup is working on improving pollinator protective label language. Many older pesticide products have less restrictive and informative language than sulfoxaflor.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Washington, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

DECISION MEMORANDUM

SUBJECT: Registration of the new active ingredient, Sulfoxaflor

FROM: Lois Rossi, Director
Registration Division (For)

TO: Steven Bradbury, PhD., Director
Office of Pesticide Programs

This memorandum recommends that you concur on the registration of the new active ingredient Sulfoxaflor. A summary of the human health and ecological risks are included in the attached Registration Decision Document. The Science Divisions have reviewed all available data and the Registration Division has concluded that the criteria for registration under FIFRA Section 3(c)(5) have been met.

RECOMMENDATIONS

I recommend for the registration the new active ingredient, Sulfoxaflor' under FIFRA Section 3(c)(5).

Concur: _____
Steven Bradbury, PhD., Director
Office of Pesticide Programs

Nonconcur: _____
Steven Bradbury, PhD., Director
Office of Pesticide Programs

Attachment: Registration Decision Document and Response to Comments Document