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 2 of 3 (PAGES 255 – 387)

GREGORY C. LOARIE
Earthjustice
50 California Street, Suite 500
San Francisco, CA 94111
T: 415.217.2000
F: 415.217.2040
E: gloarie@earthjustice.org

JANETTE K. BRIMMER
Earthjustice
705 Second Street, Suite 203
Seattle, WA 98104-1711
T: 206.343.7340
F: 206.343.1526
E: jbrimmer@earthjustice.org

Counsel for Petitioners

Index to Excerpts of Record

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.

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Chemical Safety and Pollution Prevention
Registration Division (7505C)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

NOTICE OF PESTICIDE:
_X_ Registration
___ Reregistration

(under FIFRA, as amended)

EPA Reg. Number:	Date of Issuance:
62719-623	MAY 0 6 2013

Term of Issuance:
Unconditional

Name of Pesticide Product:
Closer SC

Name and Address of Registrant (include ZIP Code):

Dow AgroSciences LLC
9330 Zionsville Rd.
Indianapolis, IN 46268

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is unconditionally registered in accordance with FIFRA section 3(c)(5) provided that you:

1. Submit and/or cite all data required for registration/registration review of your product when the Agency requires all registrants of similar products to submit such data.

2. Make the following label change before you release the product for shipment:
- Revise the EPA Registration Number to read, "EPA Reg. No 62719-623."

Signature of Approving Official:

for Meredith F. Laws

Venus Eagle, Product Manager 01
Insecticide-Rodenticide Branch, Registration Division (7505P)

Date:
MAY 0 6 2013

EPA Form 8570-6

3. Storage stability (830.6317) and corrosion characteristics (830.6320) data must be submitted within 18 months from the date of this registration notice.

4. Submit one copy of the revised final printed label for the record before you release the product for shipment.

5. Note that the CSF currently on file for this product is the basic CSF, dated 10/17/12.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions. If you have any questions, please contact Dr. Jennifer Urbanski at 703-347-0156 or urbanski.jennifer@epa.gov.

A stamped copy of the label is enclosed for your records.

Venus Eagle
Product Manager 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure

Closer™ SC

EPA Reg. No. 62719-XXX

Registration Notes:

Proposed Section 3 label.

®™Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

(Base label):

Closer™ SC

INSECTICIDE

For control or suppression of aphids, fleahoppers, plant bugs, stink bugs, whiteflies and certain psyllids, scales, and thrips in 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, potatoes, small fruit vine climbing (except fuzzy kiwifruit) except strawberry, strawberry, soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turfgrass, watercress, and wheat.

Group	4C	INSECTICIDE

Active Ingredient:
sulfoxaflor 21.8%
Other Ingredients 78.2%
Total 100.0%

Contains 2 lb active ingredient per gallon

ACCEPTED
MAY 0 6 2013
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under:

EPA. Reg. No: 62719-623

Keep Out of Reach of Children

CAUTION

Precautionary Statements

Hazard to Humans and Domestic Animals

Causes Moderate Eye Irritation

Avoid contact with eyes or clothing.

Personal Protective Equipment (PPE)

Applicators and other handlers must wear:

- Long-sleeved shirt and long pants
- Shoes plus socks

Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations

Users should:

- Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.
- Remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.

First Aid

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-992-5994 for emergency medical treatment information.

Environmental Hazards

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 or when the temperature is below 55° F at the site of application.

Refer to the Directions for Usefor crop specific restrictions and additional advisory statements 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.

Agricultural Use Requirements

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR Part 170. Refer to the label booklet under "Agricultural Use Requirements" in the Directions for Use section for information about this standard.

(Storage and Disposal for rigid containers 5 gal or less)

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.
Container Handling: Nonrefillable container. Do not reuse or refill this container.
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank and drain for 10 seconds after the flow begins to drip. Fill the container 1/4 full with water and recap. Shake for 10 seconds. Pour rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank and continue to drain for 10 seconds after the flow begins to drip. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

(Storage and Disposal for refillable rigid containers greater than 5 gal)

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.
Container Handling: Refillable container. Refill this container with pesticide only. Do not reuse this container for any other purpose.

Cleaning the container before final disposal is the responsibility of the person disposing of the container. Cleaning before refilling is the responsibility of the refiller. To clean the container before final disposal, empty the remaining contents from this container into application equipment or a mix tank. Fill the container about 10% full with water and, if possible, spray all sides while adding water. If practical, agitate vigorously or recirculate water with the pump for two minutes. Pour or pump rinsate into application equipment or rinsate collection system. Repeat this rinsing procedure two more times. Then offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

(Storage and Disposal for nonrefillable rigid containers larger than 5 gal)

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.

Pesticide Storage: Store in original container only.

Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.

Container Handling: Nonrefillable container. Do not reuse or refill this container. Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water. Replace and tighten closures. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Turn the container over onto its other end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank and continue to drain for 10 seconds after the flow begins to drip. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Refer to label booklet for Directions for Use.

Notice: Read the entire label. Use only according to label directions. **Before using this product, read Warranty Disclaimer, Inherent Risks of Use, and Limitation of Remedies at end of label booklet. If terms are unacceptable, return at once unopened.**

In case of emergency endangering health or the environment involving this product, call 1-800-992-5994.

Agricultural Chemical: Do not ship or store with food, feeds, drugs or clothing.

EPA Reg. No. 62719-XXX EPA Est. ________

Scan this code for more information at mobile.dowagro.com/closer.

Produced for
Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

NET CONTENTS ____

(Cover, shipping container):

Closer™ SC

INSECTICIDE

For control or suppression of aphids, fleahoppers, plant bugs, stink bugs, whiteflies and certain psyllids, scales, and thrips in 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, potatoes, small fruit vine climbing (except fuzzy kiwifruit) except strawberry, strawberry, soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turfgrass, watercress, and wheat.

Group	**4C**	**INSECTICIDE**

Active Ingredient:
sulfoxaflor 21.8%
Other Ingredients 78.2%
Total 100.0%

Contains 2 lb active ingredient per gallon.

Keep Out of Reach of Children

CAUTION

Agricultural Use Requirements
Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR Part 170. Refer to the label booklet under "Agricultural Use Requirements" in the Directions for Use section for information about this standard.

Refer to inside of label booklet for additional precautionary information including Directions for Use.

Notice: Read the entire label. Use only according to label directions. **Before using this product, read Warranty Disclaimer, Inherent Risks of Use, and Limitation of Remedies at end of label booklet. If terms are unacceptable, return at once unopened.**

In case of emergency endangering health or the environment involving this product, call 1-800-992-5994.

Agricultural Chemical: Do not ship or store with food, feeds, drugs or clothing.

EPA Reg. No. 62719-XXX

EPA Est. _________

Scan this code with a smart phone QR reader to access key information about this product at mobile.dowagro.com/closer. You will have access to the product label, application rates, product efficacy results, and more, all from your smart phone!

To download and install a mobile QR code reader, visit www.i-nigma.mobi on your mobile device.

Produced for
Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

NET CONTENTS ____

(Page 1 through end):

Table of Contents	Page

Precautionary Statements

Hazard to Humans and Domestic Animals

CAUTION

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Applicators and other handlers must wear:
- Long-sleeved shirt and long pants
- Shoes plus socks

Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations

Users should:
- Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.
- Remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.

First Aid

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-992-5994 for emergency medical treatment information.

Environmental Hazards

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 or when the temperature is below 55° F at the site of application.

Refer to the Directions for Use for crop specific restrictions and additional advisory statements 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.

Directions for Use

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.
Read all Directions for Use carefully before applying.

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your state or tribe, consult the agency responsible for pesticide regulation.

Agricultural Use Requirements

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR Part 170. This Standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), and restricted entry interval. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours.

PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, is:

- Coveralls
- Shoes plus socks

Non-Agricultural Use Requirements

The requirements in this box apply to uses of this product that are NOT within the scope of the Worker Protection Standard for agricultural pesticides (40 CFR Part 170). The WPS applies when this product is used to produce agricultural plants on farms, forests, nurseries, or greenhouses.

Do not enter or allow others to enter the treated area until sprays have dried.

Storage and Disposal

Do not contaminate water, food or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.

Nonrefillable rigid containers 5 gallons or less:
Container Handling: Nonrefillable container. Do not reuse or refill this container.
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank and drain for 10 seconds after the flow begins to drip. Fill the container 1/4 full with water and recap. Shake for 10 seconds. Pour rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank and continue to drain for 10 seconds after the flow begins to drip. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Refillable rigid containers larger than 5 gal:
Container Handling: Refillable container. Refill this container with pesticide only. Do not reuse this container for any other purpose.
Cleaning the container before final disposal is the responsibility of the person disposing of the container. Cleaning before refilling is the responsibility of the refiller. To clean the container before final disposal, empty the remaining contents from this container into application equipment or a mix tank. Fill the container about 10% full with water and, if possible, spray all sides while adding water. If practical, agitate vigorously or recirculate water with the pump for two minutes. Pour or pump rinsate into application equipment or rinsate collection system. Repeat this rinsing procedure two more times. Then

offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Nonrefillable rigid containers larger than 5 gal:
Container Handling: Nonrefillable container. Do not reuse or refill this container.
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water. Replace and tighten closures. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Turn the container over onto its other end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank and continue to drain for 10 seconds after the flow begins to drip. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Product Information

Carefully read, understand and follow label use rates and restrictions. Apply the amount specified in the following tables with properly calibrated aerial or ground spray equipment. Prepare only the amount of spray solution required to treat the measured acreage. The low rates may be used for light infestations of the target pests and the higher rates for moderate to heavy infestations. Closer™ SC insecticide may be applied in either dilute or concentrate sprays so long as the application equipment is calibrated and adjusted to deliver thorough, uniform coverage. Use the specified amount of Closer SC per acre regardless of the spray volume used.

Use Precautions

Integrated Pest Management (IPM) Programs
Closer SC is recommended for IPM programs in labeled crops. Apply Closer SC when field scouting indicates target pest densities have reached the economic threshold, i.e., the point at which the insect population must be reduced to avoid economic losses beyond the cost of control. Other than reducing the target pest species as a food source, Closer SC does not have a significant impact on most parasitic insects or the natural predaceous arthropod complex in treated crops, including big-eyed bugs, ladybird beetles, flower bugs, lacewings, minute pirate bugs, damsel bugs, assassin bugs, predatory mites or spiders. The feeding activities of these beneficials will aid in natural control of other insects and reduce the likelihood of secondary pest outbreaks. If Closer SC is tank mixed with any insecticide that reduces its selectivity in preserving beneficial predatory insects, the full benefit of Closer SC in an IPM program may be reduced.

Insecticide Resistance Management (IRM)
Closer SC contains a Group 4C insecticide. Insect biotypes with acquired resistance to Group 4C insecticides may eventually dominate the insect population if Group 4C insecticides are used repeatedly in the same field or area, or in successive years as the primary method of control for targeted species. This may result in partial or total loss of control of those species by Closer SC or other Group 4C insecticides.

To delay development of insecticide resistance, the following practices are recommended:
- Avoid consecutive use of insecticides on succeeding generations with the same mode of action (same insecticide group) on the same insect species.
- Consider tank mixtures or premix products containing insecticides with different modes of action (different insecticide groups) provided the products are registered for the intended use.
- Base insecticide use upon comprehensive IPM programs.

- Monitor treated insect populations in the field for loss of effectiveness.
- Do not treat seedling plants grown for transplant in greenhouses, shade houses, or field plots.
- Contact your local extension specialist, certified crop advisor, and/or manufacturer for insecticide resistance management and/or IPM recommendations for the specific site and resistant pest problems.
- For further information or to report suspected resistance, you may contact Dow AgroSciences by calling 800-258-3033.

Mixing Directions

Application Rate Reference Table

Application Rate of Closer SC (fl oz/acre)	Active Ingredient Equivalent (lb ai/acre)
0.75	0.012
1.5	0.023
2	0.031
2.75	0.043
3.5	0.061
4.25	0.066
4.5	0.070
5.75	0.09

Closer SC – Alone
Fill the spray tank with water to about 1/2 of the required spray volume. Start agitation and add the required amount of Closer SC. Continue agitation while mixing and filling the spray tank to the required spray volume. Maintain sufficient agitation during application to ensure uniformity of the spray mix. Do not allow water or spray mixture to back-siphon into the water source.

Closer SC - Tank Mix
Closer SC is believed to be compatible with most commonly used agricultural fungicides, insecticides, growth regulators, foliar fertilizers and spray adjuvants. However, whenever preparing a new tank mix, always conduct a compatibility test by mixing proportional amounts of all spray ingredients in a test vessel (jar). Shake the mixture vigorously and allow it to stand for 15 minutes. Rapid precipitation of the ingredients and failure to re-suspend when shaken indicates that the mixture is incompatible and should not be applied.

Mixing Order for Tank Mixes: Fill the spray tank with water to 1/4 to 1/3 of the required spray volume. Start agitation. Add different formulation types in the order indicated below, allowing time for complete dispersion and mixing after addition of each product. Allow extra dispersion and mixing time for dry flowable products.

Add different formulation types in the following order:
1. Water dispersible granules
2. Wettable powders
3. Closer SC and other aqueous suspensions

Maintain agitation and fill spray tank to 3/4 of total spray volume. Then add:
4. Emulsifiable concentrates and water-based solutions
5. Spray adjuvants, surfactants and oils
6. Foliar fertilizers

Finish filling the spray tank. Maintain continuous agitation during mixing, final filling and throughout application. If spraying and agitation must be stopped before the spray tank is empty, the materials may settle to the bottom. Settled materials must be resuspended before spraying is resumed. A sparger agitator is particularly useful for this purpose.

Premixing: Dry and flowable formulations may be premixed with water (slurried) and added to the spray tank through a 20 to 35 mesh screen. This procedure assures good initial dispersion of these formulation types.

Application Directions

Not for Residential Use

Proper application techniques help ensure thorough spray coverage and correct dosage for optimum insect control. Apply Closer SC as a foliar spray at the rate indicated for target pest. The following directions are provided for ground and aerial application of Closer SC. Attention should be given to sprayer speed and calibration, wind speed, and foliar canopy to ensure adequate spray coverage.

Spray Drift Management

Wind: To reduce off-target drift and achieve maximum performance, apply when wind velocity favors on-target product deposition.

Temperature Inversions: Do not make ground or aerial applications during a temperature inversion. Temperature inversions are characterized by stable air and increasing temperatures with height above the ground. Mist or fog may indicate the presence of an inversion in humid areas. The applicator may detect the presence of an inversion by producing smoke and observing a smoke layer near the ground surface.

Droplet Size: Use only medium or coarser spray nozzles (for ground and non-ULV aerial application) according to ASABE (S-572.1) definition for standard nozzles. In conditions of low humidity and high temperatures, applicators should use a coarser droplet size except where indicated for specific crops.

Ground Application

To prevent drift from groundboom applications, apply using a nozzle height of no more than 4 feet above the ground or crop canopy. Shut off the sprayer when turning at row ends. Risk of exposure to sensitive aquatic areas can be reduced by avoiding applications when wind directions are toward the aquatic area.

Airblast Sprayer: When using an airblast sprayer, coverage is also improved by operation of the sprayer at ground speeds that assure that the air volume within the tree canopy is completely replaced by the output from the airblast sprayer. Making applications in an alternate row middle pattern may result in less than satisfactory coverage and poor performance in conditions of high pest infestation levels, extremely large trees and/or dense foliage. For airblast applications, turn off outward pointing nozzles at row ends and when spraying the outer two rows. To minimize spray loss over the top in orchard applications, spray must be directed into the canopy.

Row Crop Application

Use calibrated power-operated ground spray equipment capable of providing uniform coverage of the target crop. Orient the boom and nozzles to obtain uniform crop coverage. Use a minimum of 5 to 10 gallons per acre, increasing volume with crop size and/or pest pressure. Use hollow cone, twin jet flat fan nozzles or other atomizer suitable for insecticide spraying to provide a medium to coarser spray quality (per ASABE S-572.1, see nozzle catalogs). Under certain conditions, drop nozzles may be required to obtain complete coverage of plant surfaces. Follow manufacturer's specifications for ideal nozzle spacing and spray pressure. Minimize boom height to optimize uniformity of coverage and maximize deposition (optimize on-target deposition) to reduce drift.

Orchard/Grove Spraying Application

Dilute Spray Application: This application method is based upon the premise that all plant parts are thoroughly wetted, to the point of runoff, with spray solution. To determine the number of gallons of dilute spray required per acre, contact your state agricultural experiment station, certified pest control advisor, or extension specialist for assistance.

Concentrate Spray Application: This application method is based upon the premise that all the plant parts are uniformly covered with spray solution but not to the point of runoff as with a dilute spray. Instead, a lower spray volume is used to deliver the same application rate per acre as used for the dilute spray.

Aerial Application

Apply in a minimum spray volume of 3 gallons per acre. Mount the spray boom on the aircraft so as to minimize drift caused by wing tip or rotor vortices. Use the minimum practical boom length and do not exceed 75% of the wing span or 80% of the rotor diameter. Flight speed and nozzle orientation must be considered in determining droplet size. Spray must be released at the lowest height consistent with pest control and flight safety. Do not release spray at a height greater than 10 feet above the crop canopy unless a greater height is required for aircraft safety. When applications are made with a crosswind, the swath will be displaced downwind. The applicator must compensate for this displacement at the downwind edge of the application area by adjusting the path of the aircraft upwind.

Spray Adjuvants

The addition of agricultural adjuvants to sprays of Closer SC may improve initial spray deposits, redistribution and weatherability. Select adjuvants that are recommended and registered for your specific use pattern and follow their use directions. When an adjuvant is to be used with this product, Dow AgroSciences recommends the use of a Chemical Producers and Distributors Association certified adjuvant. Always add adjuvants last in the mixing process.

Chemigation Application

Closer SC may be applied through properly equipped chemigation systems for insect control in potatoes. Do not apply Closer SC by chemigation to other crops.

Use Directions for Chemigation: Closer SC may be applied through overhead sprinkler irrigation systems that will apply water uniformly, including center pivot, lateral move, end tow, side (wheel) roll, traveler, solid set, micro sprinkler, or hand move. Do not apply this product through any other type of irrigation system. Sprinkler systems that deliver a low coefficient of uniformity such as certain water drive units are not recommended.

For continuously moving systems, the mixture containing Closer SC must be injected continuously and uniformly into the irrigation water line as the sprinkler is moving. If continuously moving irrigation equipment is used, apply in no more than 0.25 inch of water. For irrigation systems that do not move during operation, apply in no more than 0.25 inch of irrigation immediately before the end of the irrigation cycle.

Chemigation Preparation: The following use directions are to be followed when this product is applied through irrigation systems. Thoroughly clean the chemigation system and tank of any fertilizer or chemical residues, and dispose of the residues according to state and federal laws. Flush the injection system with soap or a cleaning agent and water. Determine the amount of Closer SC needed to cover the desired acreage. Mix according to instructions in the Mixing Directions section above. Continually agitate the mixture during mixing and application.

Chemigation Equipment Calibration: In order to calibrate the irrigation system and injector to apply the mixture containing Closer SC, determine the following: 1) Calculate the number of acres irrigated by the system; 2) Calculate the amount of product required and premix; 3) Determine the irrigation rate and determine the number of minutes for the system to cover the intended treatment area; 4) Calculate the total gallons of insecticide mixture needed to cover the desired acreage. Divide the total gallons of insecticide mixture needed by the number of minutes (minus time to flush out) to cover the treatment area. This value equals the gallons per minute output that the injector or eductor must deliver. Convert the gallons per minute to milliliters or ounces per minute if needed. Calibrate the injector system with the system in operation at the desired irrigation rate. It is suggested that the injection pump/system be calibrated at least twice before operation, and the system should be monitored during operation.

Chemigation Operation: Start the water pump and irrigation system, and let the system achieve the desired pressure and speed before starting the injector. Check for leaks and uniformity and make repairs before any chemigation takes place. Start the injection system and calibrate according to manufacturer's specifications. This procedure is necessary to deliver the desired rate per acre in a uniform manner. When the application is finished, allow the entire irrigation and injection system to be thoroughly flushed clean before stopping the system.

Chemigation Precautions:

- Lack of effectiveness or illegal pesticide residues in the crop can result from non-uniform distribution of treated water.
- If you have questions about calibration, contact state extension service specialists, equipment manufacturers or other experts.
- Do not connect an irrigation system used for pesticide application (including greenhouse systems) to a public water system unless the pesticide label-prescribed safety devices for public water systems are in place with current certification. Specific local regulations may apply and must be followed.
- A person knowledgeable of the chemigation system and responsible for its operation, or under the supervision of the responsible person, shall operate the system and make necessary adjustments should the need arise and continuously monitor the injection.
- Do not apply when wind speed favors drift beyond the area intended for treatment. End guns must be turned off during the application if they irrigate nontarget areas.
- Do not allow irrigation water to collect or run off and pose a hazard to livestock, wells, or adjoining crops.
- Do not enter treated area during the reentry interval specified in the Agricultural Use Requirements section of this label unless required PPE is worn.
- Do not apply through sprinkler systems that deliver a low coefficient of uniformity such as certain water drive units.

Chemigation Specific Equipment Requirements:

- The system must contain an air gap or approved backflow prevention device, or approved functional check valve, vacuum relief valve (including inspection port), and low-pressure drain appropriately located on the irrigation pipeline to prevent water source contamination from back flow. Refer to the American Society of Agricultural Engineer's Engineering Practice 409 for more information or state specific regulations.
- The pesticide injection line must contain a functional, automatic, quick-closing check valve to prevent the flow of fluid back toward the injection chemical supply.
- A pesticide injection pump must also contain a functional interlock, e.g., mechanical or electrical to shut off chemical supply when the irrigation system is either automatically or manually shut down.
- The system must contain functional interlocking controls to automatically shut off the pesticide injection when the water pressure drops too low or water flow stops.
- Use of public water supply requires approval of a backflow prevention device or air gap (preferred) by both state and local authorities.
- Systems must use a metering device, such as a positive displacement injection pump (or flow meter on eductor) effectively designed and constructed of materials that are compatible with pesticides and capable of being fitted with a system interlock. An electric powered pump must meet Section 675 for "Electrically Driven or Controlled Irrigation Machines" NEC 70.
- To insure uniform mixing of the insecticide in the water line, inject the mixture in the center of the pipe diameter or just ahead of an elbow or tee in the irrigation line so that the turbulence created at those points will assist in mixing. The injection point must be located after all backflow prevention devices on the water line.
- The tank holding the insecticide mixture should be free of rust, fertilizer, sediment, and foreign material, and equipped with an in-line strainer situated between the tank and the injection point.

Rotational Crop Restrictions

The following rotational crops may be planted at intervals defined below following the final application of Closer SC at specified rates for a registered use.

Crop	Re-Planting Interval
crops registered use	no restrictions
all other crops grown for food or feed	30 days

Use Directions

Barley, Triticale and Wheat

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids greenbug	1.0 – 1.5 (0.016 – 0.023 lb ai/acre)
Russian wheat aphid	1.5 – 2.75 (0.023 – 0.043 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:

- **Preharvest Interval:** Do not apply within 14 days of grain or straw harvest or within 7 days of grazing, or forage, fodder, or hay harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than two applications per crop.
- Do not apply more than a total of 5.75 fl oz of Closer SC (0.09 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall..

Brassica (Cole) Leafy Vegetables (Crop Group 5)[1]

[1]*Brassica* (cole) leafy vegetables (crop group 5) including broccoli, broccoli raab, Brussels sprouts, cabbage, cauliflower, cavalo, Chinese broccoli (gia lon), Chinese cabbage (bok choy), Chinese cabbage (napa), Chinese mustard cabbage (gai choy), collards, kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens, white flowering broccoli

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.0 (0.023 – 0.031 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	4.25 – 5.75 (0.066 – 0.09 lb

	ai/acre)
thrips (suppression only)	5.75 (0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 3 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Bulb Vegetables (Crop Group 3-07)[1]

[1]Bulb vegetables (crop group 3-07) including beltsville bunching onion, bulb daylilly, bulb fritillaria, bulb garlic, bulb lily, bulb onion, bulb shallot, Chinese bulb onion, Chinese fresh leaf chive, elegans hosta, fresh leaf chive, fresh leaf shallot, fresh onion, garlic, great-headed bulb garlic, green onion, kurrat, lady's leek, leek, leaf fritillaria, macrostem onion, pearl onion, potato bulb onion, serpent bulb garlic, tree onion tops, Welsh onion, wild leek, and cultivars, varieties, and/or hybrids of these

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
onion thrips (suppression only)	5.75 (0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than three applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall..

Canola (Rapeseed) (Subgroup 20A)[1]

[1]Canola (rapeseed) (subgroup 20A) including borage, canola, crambe, cuphea, echium, flax seed, gold of pleasure, hare's ear mustard, lesquerella, lunaria, meadowfoam, milkweed, mustard seed, oil radish, poppy seed, rapeseed, sesame, sweet rocket, and cultivars, varieties and/or hybrids of these

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)

aphids	1.0 – 1.5 (0.016 – 0.023 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 14 days of grain, straw, forage, fodder, or hay harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than two applications per year.
- Do not apply more than a total of 3.0 fl oz of Closer SC (0.046 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Citrus (Crop Group 10)[1]

[1]Citrus (crop group 10) including citrus citron, grapefruit, kumquat, lemon, lime, orange, tangelo, tangerine, and hybrids of these

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.75 (0.023 – 0.043 lb ai/acre)
Asian citrus psyllid citrus snow scale mealybugs	2.75 – 5.75 (0.043 – 0.09 lb ai/acre)
Citrus thrips Florida red scale	5.75 (0.09 lb ai/acre)
Suppression only: California red scale citricola scale	5.75 (0.09 lb ai/acre)

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for scales to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 1 day of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per crop.

- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Only one application is allowed between 3 days before bloom and until after petal fall per year.
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Cotton

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
cotton aphid	1.5 – 2.0 (0.023 – 0.031 lb ai/acre)
cotton fleahopper	1.5 – 3.0 (0.023 – 0.046 lb ai/acre)
tarnished plant bug western tarnished plant bug	2.75 – 4.5 (0.043 – 0.07 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	4.5 (0.07 lb ai/acre)
Suppression only: thrips brown stink bug southern green stink bug	4.5 (0.07 lb ai/acre)

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations. Two applications may be required for optimum tarnished plant bug control under high pest pressure or heavy immigration of plant bugs from other crops.

Restrictions:
- **Preharvest Interval:** Do not apply within 14 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 5 days apart.
- Do not make more than four applications per acre per year.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.

Cucurbit Vegetables (Crop Group 9)[1]

[1]Cucurbit vegetables (crop group 9) including balsam apple, balsam pear, bitter melon, casaba, chayote, Chinese cucumber, Chinese okra, crenshaw melon, crookneck squash, cucumber, cucuzza, edible gourds, golden pershaw melon, hechima, honey balls, honeydew melon, hyotan, mango melon, muskmelons (cantaloupe, honeydew, etc.), Persian melon, pineapple melon, pumpkin, Santa Claus melon, scallop squash, snake melon, spaghetti squash, straightneck squash, summer squash, true cantaloupe, vegetable marrow, watermelon, winter squash, and other varieties and/or hybrids of these

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.0 (0.023 – 0.031 lb ai/acre)
silverleaf whitefly sweetpotato whitefly thrips (suppression only)	4.25 – 4.5 (0.066 – 0.07 lb ai/acre)

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 1 day of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.

Fruiting Vegetables (Crop Group 8)[1] and Okra

[1]Fruiting vegetables (crop group 8) including bell pepper, eggplant, groundcherry, hot pepper, pepino, pepper (except black), pimento, sweet pepper, tomatillo, tomato

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.0 (0.023 – 0.031 lb ai/acre)
plant bugs	2.75 – 4.5 (0.043 – 0.07 lb ai/acre)
greenhouse whitefly (outdoors) silverleaf whitefly sweetpotato whitefly thrips (suppression only)	4.25 – 4.5 (0.066 – 0.07 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 1 day of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.

Leafy Vegetables (Except *Brassica*) (Crop Group 4)[1] and Watercress

[1]Leafy vegetables (except *Brassica*) (crop group 4) including amaranth, arugula, cardoon, celery, celtuce, chervil, Chinese celery, Chinese spinach, corn salad, cos (romaine), dandelion, dock, edible-leaved chrysanthemum, endive (escarole), finochio, Florence fennel, garden cress, garden purslane, garland chrysanthemum, head lettuce, leaf lettuce, leafy amaranth, New Zealand spinach, orach, parsley, radicchio (red chicory), rhubarb, spinach, sweet anise, sweet fennel, Swiss chard, tampala, upland cress, vine spinach, winter cress, winter purslane, yellow rocket

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.0 (0.023 – 0.031 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	4.25 – 5.75 (0.066 – 0.09 lb ai/acre)
thrips (suppression only)	5.75 (0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 3 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Leaves of Root and Tuber Vegetables (Crop Group 2)[1]

[1]Leaves of root and tuber vegetables (crop group 2) including bitter cassava, black salsify, broccoli raab, carrot, celeriac (celery root), chicory, dasheen (taro), edible burdock, garden beet, hanover salad, oriental radish (daikon), parsnip, raab, raab salad, radish, rutabaga, sugar beet, sweet cassava, sweet potato, tanier, true yam, turnip, turnip-rooted chervil

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.0 (0.023 – 0.031 lb

	ai/acre)
leafhoppers	2.75 – 5.75 (0.043 – 0.09 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	4.25 – 5.75 (0.066 – 0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Ornamentals (Herbaceous and Woody) Growing Outdoors, in Nurseries (Including Conifer Seed Orchards), or in Greenhouses

(Non-residential use only)

Pests and Application Rates:

Pests	Closer SC (fl oz/gal)	Closer SC (fl oz/100 gal)	Closer SC (fl oz/acre)
aphids, such as: green peach aphid rose aphid	0.014	1.4	2.75 (0.043 lb ai/acre)
mealybugs, such as: mealybug, juniper mealybug, maple mealybug, taxus others scales, such as: carnelia scale euonymus scale fletcher scale pine needle scale others whiteflies, such as: greenhouse whitefly silverleaf whitefly	0.03	3.0	4.5 - 5.75 (0.070 – 0.09 lb ai/acre)

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.

Application Method: Dilute Closer SC in water and apply using suitable hand- or power-operated application equipment (such as tractor-mounted, portable pump-up, backpack, hydraulic, boom) in a manner to provide complete and uniform plant coverage. Two applications may be required for optimum control of whiteflies.

Closer SC may be aerially applied to commercially grown ornamentals only. Aerial or ground applications in product agriculture or directed ground applications to individual plants are permitted. Do not make aerial applications in immediate proximity of residential, commercial, government, institutional or other structures where people may be present including homes, apartments, offices, churches, schools, and businesses. Aerial applicators should evaluate conditions existing at the time of application and make appropriate adjustments to reduce drift. In urban areas, however, use is limited to directed ground applications.

Application Rate: Closer SC may be used up to a maximum labeled rate of 0.03 fl oz per gallon (3.0 fl oz per 100 gallons, 6.0 fl oz per acre) per application on trees and ornamentals as a general treatment regardless of the target insect pest. Use pest specific rates when a single insect pest or group of insect pests within a rate category is the only intended target.

Spray Volume: Attempt to penetrate dense foliage, but avoid over spraying to the point of excessive runoff. Uniform coverage of both upper and lower leaf surfaces is critical for effective insect control.

Restrictions:
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per year.
- Do not make more than two consecutive applications.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
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- Do not make more than one application during bloom. The single application during bloom must not exceed a rate of 4.5 oz (0.070 lb/ai per acre).

Pome Fruits (Crop Group 11)[1]

[1]Pome fruits (crop group 11) including apples, crabapple, loquat, mayhaw, pears, quince

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
Aphids (except woolly apple aphid) white apple leafhopper	1.5 – 2.75 (0.023 – 0.043 lb ai/acre)
plant bugs woolly apple aphid	2.75 – 5.75 (0.043 – 0.09 lb ai/acre)
pear psylla (suppression only) San Jose scale (suppression only)	5.75 (0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for San Jose scale to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.

- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Root and Tuber Vegetables (Crop Groups 1A and 1B)[1]

[1]Root and tuber vegetables (crop group 1) including bitter black salsify, carrot, celeriac, chayote (root), chicory, chufa, daikon, dasheen, edible burdock, garden beet, ginseng, horseradish, lobok, lo pak, oriental radish, parsnip, radish, red Chinese radish, red Japanese radish, rutabaga, salsify, skirret, Spanish salsify, sugar beet, turnip, turnip-rooted chervil, turnip-rooted parsley, white Chinese radish, white Japanese radish, winter radish, and other cultivars or hybrids of these

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.75 (0.023 – 0.043 lb ai/acre)
leafhoppers	2.75 – 5.75 (0.043 – 0.09 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	4.25 – 5.75 (0.066 – 0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Potatoes (Crop Groups 1C and 1D)[1]

[1]Root and tuber vegetables (crop group 1) including arracacha, arrowroot, bitter black salsify, bitter cassava, chayote (root), Chinese artichoke, chufa, daikon, dasheen, edible canna, ginger, Jerusalem artichoke, leren, lobok, lo pak, potato, radish, sweet cassava, sweet potato, tanier, true yam, turmeric, yam, yam bean, and other cultivars or hybrids of these

Pests and Application Rates:

Pests	Closer SC (oz/acre)
aphids	1.5 – 2.75 (0.023 – 0.043 lb ai/acre)

leafhoppers	2.75 – 4.5 (0.043 – 0.07 lb ai/acre)
Potato psyllid	4.0 – 4.5 (0.061 – 0.07 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	4.5 (0.07 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.

Small Fruit Vine Climbing (Except Fuzzy Kiwifruit) (Subgroup 13-07F)[1] and Low Growing Berry (Subgroup 13-07G)[2] except Strawberry

[1]Small fruit vine climbing (except fuzzy kiwifruit) (subgroup 13-07F) including amur river grape, gooseberry, grape, hardy kiwifruit, maypop, schisandra berry, and cultivars, varieties and/or hybrids of these

[2]Low growing berry (subgroup 13-07G) including bearberry, bilberry, lowbush blueberry, cloudberry, cranberry, lingonberry, muntries, partridgeberry, and cultivars, varieties and/or hybrids of these

Pests and Application Rates:

Pests	**Closer SC (fl oz/acre)**
grape leafhopper mealybugs plant bugs	2.75 – 5.75 (0.043 – 0.09 lb ai/acre)
thrips (suppression)	5.75 (0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest of small fruit vine climbing (except fuzzy kiwifruit) and within 1 day of harvest of low growing berry.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall..

Strawberry

Pests and Application Rates:

Pests	Closer SC (oz/acre)
plant bugs	2.75 – 4.5 (0.043 – 0.07 lb ai/acre)
thrips (suppression only)	4.5 (0.07 lb ai/acre)

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 1 day of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.

Soybean

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
soybean aphid	1.5 – 2.0 (0.023 – 0.031 lb ai/acre)
Suppression only: brown stink bug southern green stink bug	4.5 (0.07 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of grain, forage or hay harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.

- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- No more than two applications may be made to soybean forage.

Stone Fruits (Crop Group 12)[1]

[1]Stone fruits (crop group 12) including apricot, nectarine, peach, plum, prune, sweet cherry, tart cherry

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.75 (0.023 – 0.043 lb ai/acre)
San Jose scale (suppression only) western flower thrips (suppression only)	5.75 (0.09 ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for San Jose scale to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall..

Succulent, Edible Podded, and Dry Beans[1]

[1]Succulent, edible podded, and dry beans including adzuki bean, asparagus bean, bean, blackeyed pea, broad bean, chickpea, Chinese longbean, cowpea, fava bean, field bean, garbanzo bean, grain lupine, green lima bean, jackbean, kidney bean, lablab bean, lima bean, moth bean, mung bean, navy bean, pinto bean, rice bean, runner bean, snap bean, soybean (immature seed), sweet lupine, sword bean, tepary bean, wax bean, white lupine, white sweet lupine, yardlong bean

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.0 (0.023 – 0.031 lb ai/acre)
plant bugs	2.75 – 4.5 (0.043 – 0.07 lb ai/acre)
brown stink bug (suppression only) southern green stink bug thrips (suppression only)	4.5 (0.07 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.

Tree Nuts (Crop Group 14)[1] and Pistachio

[1]Tree nuts (crop group 14) including almonds, cashew, chestnut, filbert (hazelnut), macadamia nut, pecan, walnut

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids	1.5 – 2.75 (0.023 – 0.045 lb ai/acre)
San Jose scale (suppression only)	5.75 (0.09 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for San Jose scale to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall..

Turfgrass

(For application only to commercial sod farms and grass grown for seed)

Pests and Application Rates:

Pests	Closer SC (fl oz/acre)
aphids (greenbug)	2.75 (0.043 lb ai/acre)
chinch bugs	5.75 (0.09 lb ai/acre)

Application Method: Dilute Closer SC in water and apply using suitable hand- or power-operated application equipment (such as tractor-mounted, portable pump-up, backpack, hydraulic, boom, turf "spray gun") in a manner to provide complete and uniform plant coverage.

Restrictions:
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 17 fl oz of Closer SC (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not feed treated grass cuttings (hay) or seed screenings to livestock or use hay for livestock bedding.
- Do not apply to golf courses, parks, playgrounds, athletic fields or residential lawns.
- Do not make aerial applications to turfgrass.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Terms and Conditions of Use

If terms of the following Warranty Disclaimer, Inherent Risks of Use, and Limitation of Remedies are not acceptable, return unopened package at once to the seller for a full refund of purchase price paid. Otherwise, use by the buyer or any other user constitutes acceptance of the terms under Warranty Disclaimer, Inherent Risks of Use and Limitation of Remedies.

Warranty Disclaimer

Dow AgroSciences warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated on the label when used in strict accordance with the directions, subject to the inherent risks set forth below. Dow AgroSciences MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER EXPRESS OR IMPLIED WARRANTY.

Inherent Risks of Use

It is impossible to eliminate all risks associated with use of this product. Plant injury, lack of performance, or other unintended consequences may result because of such factors as use of the product contrary to label instructions (including conditions noted on the label, such as unfavorable temperature, soil conditions, etc.), abnormal conditions (such as excessive rainfall, drought, tornadoes, hurricanes), presence of other materials, the manner of application, or other factors, all of which are beyond the control of Dow AgroSciences or the seller. To the extent consistent with applicable law all such risks shall be assumed by buyer.

Limitation of Remedies

To the extent permitted by law, the exclusive remedy for losses or damages resulting from this product (including claims based on contract, negligence, strict liability, or other legal theories), shall be limited to, at Dow AgroSciences' election, one of the following:

1. Refund of purchase price paid by buyer or user for product bought, or
2. Replacement of amount of product used

Dow AgroSciences shall not be liable for losses or damages resulting from handling or use of this product unless Dow AgroSciences is promptly notified of such loss or damage in writing. In no case shall Dow AgroSciences be liable for consequential or incidental damages or losses.

The terms of the Warranty Disclaimer, Inherent Risks of Use, and Limitation of Remedies cannot be varied by any written or verbal statements or agreements. No employee or sales agent of Dow AgroSciences or the seller is authorized to vary or exceed the terms of the Warranty Disclaimer or Limitation of Remedies in any manner.

EPA accepted __/__/__

U.S. ENVIRONMENTAL PROTECTION AGENCY Office of Chemical Safety and Pollution Prevention Registration Division (7505C) 1200 Pennsylvania Ave., N.W. Washington, D.C. 20460		**EPA Reg. Number:** 62719-625	**Date of Issuance:** MAY 06 2013
NOTICE OF PESTICIDE: _X_ Registration __ Reregistration (under FIFRA, as amended)		**Term of Issuance:** Unconditional	
		Name of Pesticide Product: Transform WG	

Name and Address of Registrant (include ZIP Code):

Dow AgroSciences LLC
9330 Zionsville Rd.
Indianapolis, IN 46268

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is unconditionally registered in accordance with FIFRA section 3(c)(5) provided that you:

1. Submit and/or cite all data required for registration/registration review of your product when the Agency requires all registrants of similar products to submit such data.

2. Make the following label change before you release the product for shipment:
   - Revise the EPA Registration Number to read, "EPA Reg. No 62719-625."

Signature of Approving Official: Meredith F. Laws for Venus Eagle, Product Manager 01 Insecticide-Rodenticide Branch, Registration Division (7505P)	**Date:** MAY 06 2013

EPA Form 8570-6

3. Storage stability (830.6317) and corrosion characteristics (830.6320) data must be submitted within 18 months from the date of this registration notice.

4. Submit one copy of the revised final printed label for the record before you release the product for shipment.

5. Note that the CSF currently on file for this product is the basic CSF, dated 6/30/10.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions. If you have any questions, please contact Dr. Jennifer Urbanski at 703-347-0156 or urbanski.jennifer@epa.gov.

A stamped copy of the label is enclosed for your records.

Venus Eagle
Product Manager 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure

Transform™ WG

EPA Reg. No. 62719-XXX

Registration Notes:

Proposed Section 3 label.

®™Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

(Base label):

Transform™ WG

INSECTICIDE

For control or suppression of aphids, fleahoppers, plant bugs, stink bugs, whiteflies and certain psyllids, scales, and thrips in 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, potatoes, small fruit vine climbing (except fuzzy kiwifruit) except strawberry, strawberry, soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turfgrass, watercress, and wheat.

Group	4C	INSECTICIDE

ACCEPTED
MAY 0 6 2013
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under:
EPA. Reg. No: 62719-625

Active Ingredient:
sulfoxaflor 50%
Other Ingredients 50%
Total 100%

Contains 50% active ingredient on a weight basis.

Keep Out of Reach of Children

DANGER PELIGRO

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label, find someone to explain it to you in detail.)

Precautionary Statements

Hazard to Humans and Domestic Animals

Corrosive. Causes Irreversible Eye Damage • Harmful If Swallowed

Do not get in eyes or on clothing.

Personal Protective Equipment (PPE)

Applicators and other handlers must wear:
- Long-sleeved shirt and long pants
- Shoes plus socks
- Protective eyewear

Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this product's concentrate. Do not reuse them. Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations

Users should:

- Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.
- Remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
- Remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

First Aid

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.
If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage.

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-992-5994 for emergency medical treatment information.

Environmental Hazards

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 or when the temperature is below 55° F at the site of application.

Refer to the Directions for Use for crop specific restrictions and additional advisory statements 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.

Agricultural Use Requirements

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR Part 170. Refer to the label booklet under "Agricultural Use Requirements" in the Directions for Use section for information about this standard.

(Storage and Disposal for rigid containers 5 gal or less)

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.
Container Handling: Nonrefillable container. Do not reuse or refill this container.
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water and recap. Shake for 10 seconds. Pour rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at

least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

(Storage and Disposal for nonrigid containers any size)

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.
Container Handling: Nonrefillable container. Do not reuse or refill this container. Completely empty bag into application equipment. Then offer for recycling if available, or dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

(Storage and Disposal for refillable rigid containers greater than 5 gal)

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.
Container Handling: Refillable container. Refill this container with pesticide only. Do not reuse this container for any other purpose.
Cleaning the container before final disposal is the responsibility of the person disposing of the container. Cleaning before refilling is the responsibility of the refiller. To clean the container before final disposal, empty the remaining contents from this container into application equipment or a mix tank. Fill the container about 10% full with water and, if possible, spray all sides while adding water. If practical, agitate vigorously or recirculate water with the pump for two minutes. Pour or pump rinsate into application equipment or rinsate collection system. Repeat this rinsing procedure two more times. Then offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

(Storage and Disposal for nonrefillable rigid containers larger than 5 gal)

Storage and Disposal

Do not contaminate water, food, or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.
Container Handling: Nonrefillable container. Do not reuse or refill this container.
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water. Replace and tighten closures. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Turn the container over onto its other end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Refer to label booklet for Directions for Use.

Notice: Read the entire label. Use only according to label directions. **Before using this product, read**

Warranty Disclaimer, Inherent Risks of Use, and Limitation of Remedies at end of label booklet. If terms are unacceptable, return at once unopened.

In case of emergency endangering health or the environment involving this product, call 1-800-992-5994.

Agricultural Chemical: Do not ship or store with food, feeds, drugs or clothing.

EPA Reg. No. 62719-XXX EPA Est. ________

Scan this code with a smart phone QR reader to access key information about this product at mobile.dowagro.com/transform. You will have access to the product label, application rates, product efficacy results, and more, all from your smart phone!

To download and install a mobile QR code reader, visit www.i-nigma.mobi on your mobile device.

Produced for
Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

NET WEIGHT ____

(Cover, shipping container):

Transform™ WG

INSECTICIDE

For control or suppression of aphids, fleahoppers, plant bugs, stink bugs, whiteflies and certain psyllids, scales, and thrips in 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, potatoes, small fruit vine climbing (except fuzzy kiwifruit) except strawberry, strawberry, soybean, stone fruits, succulent, edible podded, and dry beans, tree nuts, triticale, turfgrass, watercress, and wheat.

Group	4C	INSECTICIDE

Active Ingredient:
sulfoxaflor 50%
Other Ingredients 50%
Total 100%

Contains 50% active ingredient on a weight basis.

Keep Out of Reach of Children

DANGER PELIGRO

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle. (If you do not understand the label, find someone to explain it to you in detail.)

Agricultural Use Requirements

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR Part 170. Refer to the label booklet under "Agricultural Use Requirements" in the Directions for Use section for information about this standard.

Refer to inside of label booklet for additional precautionary information including Directions for Use.

Notice: Read the entire label. Use only according to label directions. **Before using this product, read Warranty Disclaimer, Inherent Risks of Use, and Limitation of Remedies at end of label booklet. If terms are unacceptable, return at once unopened.**

In case of emergency endangering health or the environment involving this product, call 1-800-992-5994.

Agricultural Chemical: Do not ship or store with food, feeds, drugs or clothing.

EPA Reg. No. 62719-XXX EPA Est. _________

Scan this code with a smart phone QR reader to access key information about this product at mobile.dowagro.com/transform. You will have access to the product label, application rates, product efficacy results, and more, all from your smart phone!

To download and install a mobile QR code reader, visit www.i-nigma.mobi on your mobile device.

Produced for
Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

NET WEIGHT ____

(Page 1 through end):

Table of Contents

Precautionary Statements

Hazard to Humans and Domestic Animals

DANGER

Corrosive. Causes Irreversible Eye Damage • Harmful If Swallowed

Do not get in eyes or on clothing.

Personal Protective Equipment (PPE)

Applicators and other handlers must wear:

- Long-sleeved shirt and long pants
- Shoes plus socks
- Protective eyewear

Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this product's concentrate. Do not reuse them. Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations

Users should:

- Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.
- Remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
- Remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

First Aid

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage.

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-992-5994 for emergency medical treatment information.

Environmental Hazards

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 or when the temperature is below 55° F at the site of application.

Refer to the Directions for Use for crop specific restrictions and additional advisory statements 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.

Directions for Use

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.
Read all Directions for Use carefully before applying.

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your state or tribe, consult the agency responsible for pesticide regulation.

Agricultural Use Requirements

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR Part 170. This Standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), and restricted entry interval. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 24 hours.

PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, is:
- Coveralls
- Shoes plus socks

Non-Agricultural Use Requirements

The requirements in this box apply to uses of this product that are NOT within the scope of the Worker Protection Standard for agricultural pesticides (40 CFR Part 170). The WPS applies when this product is used to produce agricultural plants on farms, forests, nurseries, or greenhouses.

Do not enter or allow others to enter the treated area until sprays have dried.

Storage and Disposal

Do not contaminate water, food or feed by storage or disposal.
Pesticide Storage: Store in original container only.
Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.

Nonrefillable rigid containers 5 gallons or less:
Container Handling: Nonrefillable container. Do not reuse or refill this container.
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water and recap. Shake for 10 seconds. Pour rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Nonrefillable nonrigid containers:
Container Handling: Nonrefillable container. Do not reuse or refill this container. Completely empty bag into application equipment. Then offer for recycling if available, or dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Refillable rigid containers larger than 5 gal:
Container Handling: Refillable container. Refill this container with pesticide only. Do not reuse this container for any other purpose.
Cleaning the container before final disposal is the responsibility of the person disposing of the container. Cleaning before refilling is the responsibility of the refiller. To clean the container before final disposal, empty the remaining contents from this container into application equipment or a mix tank. Fill the container about 10% full with water and, if possible, spray all sides while adding water. If practical, agitate vigorously or recirculate water with the pump for two minutes. Pour or pump rinsate into application equipment or rinsate collection system. Repeat this rinsing procedure two more times. Then offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Nonrefillable rigid containers larger than 5 gal:
Container Handling: Nonrefillable container. Do not reuse or refill this container.
Triple rinse or pressure rinse container (or equivalent) promptly after emptying. **Triple rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water. Replace and tighten closures. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Turn the container over onto its other end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. **Pressure rinse** as follows: Empty the remaining contents into application equipment or a mix tank. Hold container upside down over application equipment or mix tank or collect rinsate for later use or disposal. Insert pressure rinsing nozzle in the side of the container, and rinse at about 40 psi for at least 30 seconds. Drain for 10 seconds after the flow begins to drip. Then offer for recycling if available, or puncture and dispose of in a sanitary landfill, or by incineration, or by other procedures allowed by state and local authorities.

Product Information

Carefully read, understand and follow label use rates and restrictions. Apply the amount specified in the following tables with properly calibrated aerial or ground spray equipment. Prepare only the amount of spray solution required to treat the measured acreage. The low rates may be used for light infestations of the target pests and the higher rates for moderate to heavy infestations. Transform™ WG insecticide may be applied in either dilute or concentrate sprays so long as the application equipment is calibrated and adjusted to deliver thorough, uniform coverage. Use the specified amount of Transform WG per acre regardless of the spray volume used.

Use Precautions

Integrated Pest Management (IPM) Programs

Transform WG is recommended for IPM programs in labeled crops. Apply Transform WG when field scouting indicates target pest densities have reached the economic threshold, i.e., the point at which the insect population must be reduced to avoid economic losses beyond the cost of control. Other than reducing the target pest species as a food source, Transform WG does not have a significant impact on most parasitic insects or the natural predaceous arthropod complex in treated crops, including big-eyed bugs, ladybird beetles, flower bugs, lacewings, minute pirate bugs, damsel bugs, assassin bugs, predatory mites or spiders. The feeding activities of these beneficials will aid in natural control of other insects and reduce the likelihood of secondary pest outbreaks. If Transform WG is tank mixed with any insecticide that reduces its selectivity in preserving beneficial predatory insects, the full benefit of Transform WG in an IPM program may be reduced.

Insecticide Resistance Management (IRM)
Transform WG contains a Group 4C insecticide. Insect biotypes with acquired resistance to Group 4C insecticides may eventually dominate the insect population if Group 4C insecticides are used repeatedly in the same field or area, or in successive years as the primary method of control for targeted species. This may result in partial or total loss of control of those species by Transform WG or other Group 4C insecticides.

To delay development of insecticide resistance, the following practices are recommended:
- Avoid consecutive use of insecticides on succeeding generations with the same mode of action (same insecticide subgroup, 4C) on the same insect species.
- Consider tank mixtures or premix products containing insecticides with different modes of action (different insecticide groups) provided the products are registered for the intended use.
- Base insecticide use upon comprehensive IPM programs.
- Monitor treated insect populations in the field for loss of effectiveness.
- Do not treat seedling plants grown for transplant in greenhouses, shade houses, or field plots.
- Contact your local extension specialist, certified crop advisor, and/or manufacturer for insecticide resistance management and/or IPM recommendations for the specific site and resistant pest problems.
- For further information or to report suspected resistance, you may contact Dow AgroSciences by calling 800-258-3033.

Mixing Directions

Application Rate Reference Table

Application Rate of Transform WG (oz/acre)	Active Ingredient Equivalent (lb ai/acre)
0.75	0.023
1	0.031
1.5	0.047
1.75	0.055
2.25	0.071
2.75	0.086

Transform WG – Alone
Fill the spray tank with water to about 1/2 of the required spray volume. Start agitation and add the required amount of Transform WG. Continue agitation while mixing and filling the spray tank to the required spray volume. Maintain sufficient agitation during application to ensure uniformity of the spray mix. Do not allow water or spray mixture to back-siphon into the water source.

Transform WG - Tank Mix
When tank mixing Transform WG with other materials, conduct compatibility test (jar test) using relative proportions of the tank mix ingredients prior to mixing ingredients in the spray tank. If foliar fertilizers are used, the jar test should be repeated with each batch of fertilizer utilizing the mixing water source. Vigorous, continuous agitation during mixing, filling and throughout application is required for all tank mixes. Sparger pipe agitators generally provide the most effective agitation in spray tanks. To prevent foaming in the spray tank, avoid stirring or splashing air into the spray mixture.

Mixing Order for Tank Mixes: Fill the spray tank with water to 1/4 to 1/3 of the required spray volume. Start agitation. Add different formulation types in the order indicated below, allowing time for complete dispersion and mixing after addition of each product. Allow extra dispersion and mixing time for dry flowable products.

Add different formulation types in the following order:
1. Transform WG and other water dispersible granules

2. Wettable powders
3. Suspension concentrates and other liquids

Maintain agitation and fill spray tank to 3/4 of total spray volume. Then add:
4. Emulsifiable concentrates and water-based solutions
5. Spray adjuvants, surfactants and oils
6. Foliar fertilizers

Finish filling the spray tank. Maintain continuous agitation during mixing, final filling and throughout application. If spraying and agitation must be stopped before the spray tank is empty, the materials may settle to the bottom. Settled materials must be resuspended before spraying is resumed. A sparger agitator is particularly useful for this purpose.

Premixing: Dry and flowable formulations may be premixed with water (slurried) and added to the spray tank through a 20 to 35 mesh screen. This procedure assures good initial dispersion of these formulation types.

Application Directions

Not for Residential Use

Do not apply Transform WG in greenhouses or other enclosed structures used for growing crops.

Proper application techniques help ensure thorough spray coverage and correct dosage for optimum insect control. Apply Transform WG as a foliar spray at the rate indicated for target pest. The following directions are provided for ground and aerial application of Transform WG. Attention should be given to sprayer speed and calibration, wind speed, and foliar canopy to ensure adequate spray coverage.

Spray Drift Management

Wind: To reduce off-target drift and achieve maximum performance, apply when wind velocity favors on-target product deposition.

Temperature Inversions: Do not make ground or aerial applications during a temperature inversion. Temperature inversions are characterized by stable air and increasing temperatures with height above the ground. Mist or fog may indicate the presence of an inversion in humid areas. The applicator may detect the presence of an inversion by producing smoke and observing a smoke layer near the ground surface.

Droplet Size: Use only medium or coarser spray nozzles (for ground and non-ULV aerial application) according to ASABE (S-572.1) definition for standard nozzles. In conditions of low humidity and high temperatures, applicators should use a coarser droplet size except where indicated for specific crops.

Ground Application
To prevent drift from groundboom applications, apply using a nozzle height of no more than 4 feet above the ground or crop canopy. Shut off the sprayer when turning at row ends. Risk of exposure to sensitive aquatic areas can be reduced by avoiding applications when wind directions are toward the aquatic area.

Row Crop Application
Use calibrated power-operated ground spray equipment capable of providing uniform coverage of the target crop. Orient the boom and nozzles to obtain uniform crop coverage. Use a minimum of 5 to 10 gallons per acre, increasing volume with crop size and/or pest pressure. Use hollow cone, twin jet flat fan nozzles or other atomizer suitable for insecticide spraying to provide a fine to coarse spray quality (per ASABE S-572.1, see nozzle catalogs). Under certain conditions, drop nozzles may be required to obtain complete coverage of plant surfaces. Follow manufacturer's specifications for ideal nozzle spacing and spray pressure. Minimize boom height to optimize uniformity of coverage and maximize deposition (optimize on-target deposition) to reduce drift.

Orchard/Grove Spraying Application

Dilute Spray Application: This application method is based upon the premise that all plant parts are thoroughly wetted, to the point of runoff, with spray solution. To determine the number of gallons of dilute spray required per acre, contact your state agricultural experiment station, certified pest control advisor, or extension specialist for assistance.

Concentrate Spray Application: This application method is based upon the premise that all the plant parts are uniformly covered with spray solution but not to the point of runoff as with a dilute spray. Instead, a lower spray volume is used to deliver the same application rate per acre as used for the dilute spray.

Aerial Application

Apply in a minimum spray volume of 3 gallons per acre. Mount the spray boom on the aircraft so as to minimize drift caused by wing tip or rotor vortices. Use the minimum practical boom length and do not exceed 75% of the wing span or 80% of the rotor diameter. Flight speed and nozzle orientation must be considered in determining droplet size. Spray must be released at the lowest height consistent with pest control and flight safety. Do not release spray at a height greater than 10 feet above the crop canopy unless a greater height is required for aircraft safety. When applications are made with a crosswind, the swath will be displaced downwind. The applicator must compensate for this displacement at the downwind edge of the application area by adjusting the path of the aircraft upwind.

Spray Adjuvants

The addition of agricultural adjuvants to sprays of Transform WG may improve initial spray deposits, redistribution and weatherability. Select adjuvants that are recommended and registered for your specific use pattern and follow their use directions. When an adjuvant is to be used with this product, Dow AgroSciences recommends the use of a Chemical Producers and Distributors Association certified adjuvant. Always add adjuvants last in the mixing process.

Chemigation Application

Transform WG may be applied through properly equipped chemigation systems for insect control in potatoes. Do not apply Transform WG by chemigation to other crops.

Use Directions for Chemigation: Transform WG may be applied through overhead sprinkler irrigation systems that will apply water uniformly, including center pivot, lateral move, end tow, side (wheel) roll, traveler, solid set, micro sprinkler, or hand move. Do not apply this product through any other type of irrigation system. Sprinkler systems that deliver a low coefficient of uniformity such as certain water drive units are not recommended.

For continuously moving systems, the mixture containing Transform WG must be injected continuously and uniformly into the irrigation water line as the sprinkler is moving. If continuously moving irrigation equipment is used, apply in no more than 0.25 inch of water. For irrigation systems that do not move during operation, apply in no more than 0.25 inch of irrigation immediately before the end of the irrigation cycle.

Chemigation Preparation: The following use directions are to be followed when this product is applied through irrigation systems. Thoroughly clean the chemigation system and tank of any fertilizer or chemical residues, and dispose of the residues according to state and federal laws. Flush the injection system with soap or a cleaning agent and water. Determine the amount of Transform WG needed to cover the desired acreage. Mix according to instructions in the Mixing Directions section above. Continually agitate the mixture during mixing and application.

Chemigation Equipment Calibration: In order to calibrate the irrigation system and injector to apply the mixture containing Transform WG, determine the following: 1) Calculate the number of acres irrigated by the system; 2) Calculate the amount of product required and premix; 3) Determine the irrigation rate and determine the number of minutes for the system to cover the intended treatment area; 4) Calculate the total gallons of insecticide mixture needed to cover the desired acreage. Divide the total gallons of insecticide mixture needed by the number of minutes (minus time to flush out) to cover the treatment area. This value equals the gallons per minute output that the injector or eductor must deliver. Convert the gallons per minute to milliliters or ounces per minute if needed. Calibrate the injector system with the system in operation at the desired irrigation rate. It is suggested that the injection pump/system be calibrated at least twice before operation, and the system should be monitored during operation.

Chemigation Operation: Start the water pump and irrigation system, and let the system achieve the desired pressure and speed before starting the injector. Check for leaks and uniformity and make repairs before any chemigation takes place. Start the injection system and calibrate according to manufacturer's specifications. This procedure is necessary to deliver the desired rate per acre in a uniform manner. When the application is finished, allow the entire irrigation and injection system to be thoroughly flushed clean before stopping the system.

Chemigation Precautions:

- Lack of effectiveness or illegal pesticide residues in the crop can result from non-uniform distribution of treated water.
- If you have questions about calibration, contact state extension service specialists, equipment manufacturers or other experts.
- Do not connect an irrigation system used for pesticide application (including greenhouse systems) to a public water system unless the pesticide label-prescribed safety devices for public water systems are in place with current certification. Specific local regulations may apply and must be followed.
- A person knowledgeable of the chemigation system and responsible for its operation, or under the supervision of the responsible person, shall operate the system and make necessary adjustments should the need arise and continuously monitor the injection.
- Do not apply when wind speed favors drift beyond the area intended for treatment. End guns must be turned off during the application if they irrigate nontarget areas.
- Do not allow irrigation water to collect or run off and pose a hazard to livestock, wells, or adjoining crops.
- Do not enter treated area during the reentry interval specified in the Agricultural Use Requirements section of this label unless required PPE is worn.
- Do not apply through sprinkler systems that deliver a low coefficient of uniformity such as certain water drive units.

Chemigation Specific Equipment Requirements:

- The system must contain an air gap or approved backflow prevention device, or approved functional check valve, vacuum relief valve (including inspection port), and low-pressure drain appropriately located on the irrigation pipeline to prevent water source contamination from back flow. Refer to the American Society of Agricultural Engineer's Engineering Practice 409 for more information or state specific regulations.
- The pesticide injection line must contain a functional, automatic, quick-closing check valve to prevent the flow of fluid back toward the injection chemical supply.
- A pesticide injection pump must also contain a functional interlock, e.g., mechanical or electrical to shut off chemical supply when the irrigation system is either automatically or manually shut down.
- The system must contain functional interlocking controls to automatically shut off the pesticide injection when the water pressure drops too low or water flow stops.
- Use of public water supply requires approval of a backflow prevention device or air gap (preferred) by both state and local authorities.
- Systems must use a metering device, such as a positive displacement injection pump (or flow meter on eductor) effectively designed and constructed of materials that are compatible with pesticides and capable of being fitted with a system interlock. An electric powered pump must meet Section 675 for "Electrically Driven or Controlled Irrigation Machines" NEC 70.
- To insure uniform mixing of the insecticide in the water line, inject the mixture in the center of the pipe diameter or just ahead of an elbow or tee in the irrigation line so that the turbulence created at those

points will assist in mixing. The injection point must be located after all backflow prevention devices on the water line.
- The tank holding the insecticide mixture should be free of rust, fertilizer, sediment, and foreign material, and equipped with an in-line strainer situated between the tank and the injection point.

Rotational Crop Restrictions

The following rotational crops may be planted at intervals defined below following the final application of Transform WG at specified rates for a registered use.

Crop	Re-Planting Interval
crops registered use	no restrictions
all other crops grown for food or feed	30 days

Use Directions

Barley, Triticale and Wheat

Pests and Application Rates:

Pests	Transform WG (oz/acre)
aphids greenbug	0.5 – 0.75 (0.016 – 0.023 lb ai/acre)
Russian wheat aphid	0.75 – 1.5 (0.023 - 0.047 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 14 days of grain or straw harvest or within 7 days of grazing, or forage, fodder, or hay harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than two applications per crop.
- Do not apply more than a total of 2.8 oz of Transform WG (0.09 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Brassica (Cole) Leafy Vegetables (Crop Group 5)[1]

[1]*Brassica* (cole) leafy vegetables (crop group 5) including broccoli, broccoli raab, Brussels sprouts, cabbage, cauliflower, cavalo, Chinese broccoli (gia lon), Chinese cabbage (bok choy), Chinese cabbage (napa), Chinese mustard cabbage (gai choy), collards, kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens, white flowering broccoli

Pests and Application Rates:

Pests	Transform WG (oz/acre)
Aphids	0.75 – 1.0

	(0.023 – 0.031 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	2.0 – 2.75 (0.063 – 0.086 lb ai/acre)
thrips (suppression only)	2.75 (0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 3 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Bulb Vegetables (Crop Group 3-07)[1]

[1]Bulb vegetables (crop group 3-07) including beltsville bunching onion, bulb daylilly, bulb fritillaria, bulb garlic, bulb lily, bulb onion, bulb shallot, Chinese bulb onion, Chinese fresh leaf chive, elegans hosta, fresh leaf chive, fresh leaf shallot, fresh onion, garlic, great-headed bulb garlic, green onion, kurrat, lady's leek, leek, leaf fritillaria, macrostem onion, pearl onion, potato bulb onion, serpent bulb garlic, tree onion tops, Welsh onion, wild leek, and cultivars, varieties, and/or hybrids of these

Pests and Application Rates:

Pests	Transform WG (oz/acre)
onion thrips (suppression only)	2.75 (0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Canola (Rapeseed) (Subgroup 20A)[1]

[1]Canola (rapeseed) (subgroup 20A) including borage, canola, crambe, cuphea, echium, flax seed, gold of pleasure, hare's ear mustard, lesquerella, lunaria, meadowfoam, milkweed, mustard seed, oil radish, poppy seed, rapeseed, sesame, sweet rocket, and cultivars, varieties and/or hybrids of these

Pests and Application Rates:

Pests	Transform WG (oz/acre)
Aphids	0.5 – 0.75 (0.016 – 0.023 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 14 days of grain, straw, forage, fodder, or hay harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than two applications per year.
- Do not apply more than a total of 1.5 oz of Transform WG (0.046 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Citrus (Crop Group 10)[1]

[1]Citrus (crop group 10) including citrus citron, grapefruit, kumquat, lemon, lime, orange, tangelo, tangerine, and hybrids of these

Pests and Application Rates:

Pests	Transform WG (oz/acre)
Aphid	0.75 – 1.5 (0.023 - 0.047 lb ai/acre)
Asian citrus psyllid citrus snow scale mealybugs	1.5 – 2.75 (0.047 – 0.086 lb ai/acre)
Citrus thrips Florida red scale	2.75 (0.086 lb ai/acre)
Suppression only: California red scale citricola scale	2.75 (0.086 lb ai/acre

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for scales to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 1 day of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Only one application is allowed between 3 days before bloom and until after petal fall per year.

Cotton

Pests and Application Rates:

Pests	Transform WG (oz/acre)
cotton aphid	0.75 – 1.0 (0.023 – 0.031 lb ai/acre)
cotton fleahopper	0.75 – 1.5 (0.023 – 0.047 lb ai/acre)
tarnished plant bug western tarnished plant bug	1.5 – 2.25 (0.047 – 0.071 lb ai/acre)
sweetpotato whitefly, silverleaf whitefly	2.0 – 2.25 (0.063 – 0.071 lb ai/acre)
Suppression only: brown stink bug, southern green stink bug, thrips	2.0 – 2.25 (0.063 – 0.071 lb ai/acre)

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations. Two applications may be required for optimum tarnished plant bug control under high pest pressure or heavy immigration of plant bugs from other crops.

Restrictions:
- **Preharvest Interval:** Do not apply within 14 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 5 days apart.
- Do not make more than four applications per acre per year.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

Cucurbit Vegetables (Crop Group 9)[1]

[1]Cucurbit vegetables (crop group 9) including balsam apple, balsam pear, bitter melon, casaba, chayote, Chinese cucumber, Chinese okra, crenshaw melon, crookneck squash, cucumber, cucuzza, edible gourds, golden pershaw melon, hechima, honey balls, honeydew melon, hyotan, mango melon, muskmelons (cantaloupe, honeydew, etc.), Persian melon, pineapple melon, pumpkin, Santa Claus melon, scallop squash, snake melon, spaghetti squash, straightneck squash, summer squash, true cantaloupe, vegetable marrow, watermelon, winter squash, and other varieties and/or hybrids of these

Pests and Application Rates:

Pests	**Transform WG (oz/acre)**
Aphids	0.75 (0.023 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	2.0 – 2.25 (0.063 – 0.071 lb ai/acre)
thrips (suppression only)	2.25 (0.071 lb ai/acre)

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 1 day of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

Fruiting Vegetables (Crop Group 8)[1] and Okra

[1]Fruiting vegetables (crop group 8) including bell pepper, eggplant, groundcherry, hot pepper, pepino, pepper (except black), pimento, sweet pepper, tomatillo, tomato

Pests and Application Rates:

Pests	**Transform WG (oz/acre)**
Aphids	0.75 – 1.0 (0.023 – 0.031 lb ai/acre)
plant bugs	1.5 – 2.25 (0.047 - 0.071 lb ai/acre)
greenhouse whitefly (outdoors)	2 – 2.25 (0.063 – 0.071 lb

silverleaf whitefly sweetpotato whitefly	ai/acre)
thrips (suppression only)	2.25 (0.071 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 1 day of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

Leafy Vegetables (Except *Brassica*) (Crop Group 4)[1] and Watercress

[1]Leafy vegetables (except *Brassica*) (crop group 4) including amaranth, arugula, cardoon, celery, celtuce, chervil, Chinese celery, Chinese spinach, corn salad, cos (romaine), dandelion, dock, edible-leaved chrysanthemum, endive (escarole), finochio, Florence fennel, garden cress, garden purslane, garland chrysanthemum, head lettuce, leaf lettuce, leafy amaranth, New Zealand spinach, orach, parsley, radicchio (red chicory), rhubarb, spinach, sweet anise, sweet fennel, Swiss chard, tampala, upland cress, vine spinach, winter cress, winter purslane, yellow rocket

Pests and Application Rates:

Pests	Transform WG (oz/acre)
Aphids	0.75 – 1.0 (0.023 - 0.031 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	2.0 – 2.75 (0.063 – 0.086 lb ai/acre)
thrips (suppression only)	2.75 (0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 3 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Leaves of Root and Tuber Vegetables (Crop Group 2)[1]

[1]Leaves of root and tuber vegetables (crop group 2) including bitter cassava, black salsify, broccoli raab, carrot, celeriac (celery root), chicory, dasheen (taro), edible burdock, garden beet, hanover salad, oriental radish (daikon), parsnip, raab, raab salad, radish, rutabaga, sugar beet, sweet cassava, sweet potato, tanier, true yam, turnip, turnip-rooted chervil

Pests and Application Rates:

Pests	Transform WG (oz/acre)
Aphids	0.75 – 1.0 (0.023 – 0.031 lb ai/acre)
Leafhoppers	1.5 – 2.75 (0.047 – 0.086 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	2.0 – 2.75 (0.063 – 0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Ornamentals (Herbaceous and Woody) Growing Outdoors, in Nurseries (Including Conifer Seed Orchards), or in Greenhouses

(Non-residential use only)

Pests and Application Rates:

Pests	Transform WG (oz/gal)	Transform WG (oz/100 gal)	Transform WG (oz/acre)
aphids, such as: green peach aphid rose aphid	0.008	0.8	1.5 (0.047 lb ai/acre)
mealybugs, such as: mealybug, juniper mealybug, maple mealybug, taxus others scales, such as: carnelia scale euonymus scale fletcher scale pine needle scale others	0.013	1.4	2.25 – 2.75 (0.071 – 0.086 lb ai/acre)

whiteflies, such as: greenhouse whitefly silverleaf whitefly			

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.

Application Method: Dilute Transform WG in water and apply using suitable hand- or power-operated application equipment (such as tractor-mounted, portable pump-up, backpack, hydraulic, boom) in a manner to provide complete and uniform plant coverage. Two applications may be required for optimum control of whiteflies.

Transform WG may be aerially applied to commercially grown ornamentals only. Aerial or ground applications in product agriculture or directed ground applications to individual plants are permitted. Do not make aerial applications in immediate proximity of residential, commercial, government, institutional or other structures where people may be present including homes, apartments, offices, churches, schools, and businesses. Aerial applicators should evaluate conditions existing at the time of application and make appropriate adjustments to reduce drift. In urban areas, however, use is limited to directed ground applications.

Application Rate: Transform WG may be used up to a maximum labeled rate of 0.013 oz per gallon (1.4 oz per 100 gallons, 2.75 oz per acre) per application on trees and ornamentals as a general treatment regardless of the target insect pest. Use pest specific rates when a single insect pest or group of insect pests within a rate category is the only intended target.

Spray Volume: Attempt to penetrate dense foliage, but avoid over spraying to the point of excessive runoff. Uniform coverage of both upper and lower leaf surfaces is critical for effective insect control.

Restrictions:
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per year.
- Do not make more than two consecutive applications.
-
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not make more than one application during bloom. The single application during bloom must not exceed a rate of 2.25 oz (0.071 lb/ai per acre).

Pome Fruits (Crop Group 11)[1]

[1]Pome fruits (crop group 11) including apples, crabapple, loquat, mayhaw, pears, quince

Pests and Application Rates:

Pests	Transform WG (oz/acre)
aphids white apple leafhopper	0.75 – 1.5 (0.023 - 0.047 lb ai/acre)
plant bugs woolly apple aphid	1.5 – 2.75 (0.047 – 0.086 lb ai/acre)
pear psylla (suppression only) San Jose scale (suppression only)	2.75 (0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for San Jose scale to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Root and Tuber Vegetables (Crop Groups 1A and 1B)[1]

[1]Root and tuber vegetables (crop group 1) including bitter black salsify, carrot, celeriac, chayote (root), chicory, chufa, daikon, dasheen, edible burdock, garden beet, ginseng, horseradish, lobok, lo pak, oriental radish, parsnip, radish, red Chinese radish, red Japanese radish, rutabaga, salsify, skirret, Spanish salsify, sugar beet, turnip, turnip-rooted chervil, turnip-rooted parsley, white Chinese radish, white Japanese radish, winter radish, and other cultivars or hybrids of these

Pests and Application Rates:

Pests	Transform WG (oz/acre)
Aphids	0.75 – 1.5 (0.023 – 0.047 lb ai/acre)
Leafhoppers	1.5 – 2.75 (0.047 – 0.086 lb ai/acre)
silverleaf whitefly sweetpotato whitefly	2.0 – 2.75 (0.063 – 0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Potatoes (Crop Groups 1C and 1D)[1]

[1]Root and tuber vegetables (crop group 1) including arracacha, arrowroot, bitter black salsify, bitter cassava, chayote (root), Chinese artichoke, chufa, daikon, dasheen, edible canna, ginger, Jerusalem

artichoke, leren, lobok, lo pak, potato, radish, sweet cassava, sweet potato, tanier, true yam, turmeric, yam, yam bean, and other cultivars or hybrids of these

Pests and Application Rates:

Pests	Transform WG (oz/acre)
aphids	0.75 – 1.5 (0.023 – 0.047 lb ai/acre)
Leafhoppers	1.5 – 2.25 (0.047 – 0.071 lb ai/acre)
Potato psyllid silverleaf whitefly sweetpotato whitefly	2.0 – 2.25 (0.063 – 0.071 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Two applications may be required for optimum control of whiteflies.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

Small Fruit Vine Climbing (Except Fuzzy Kiwifruit) (Subgroup 13-07F)[1] and Low Growing Berry (Subgroup 13-07G)[2] except Strawberry

[1]Small fruit vine climbing (except fuzzy kiwifruit) (subgroup 13-07F) including amur river grape, gooseberry, grape, hardy kiwifruit, maypop, schisandra berry, and cultivars, varieties and/or hybrids of these

[2]Low growing berry (subgroup 13-07G) including bearberry, bilberry, lowbush blueberry, cloudberry, cranberry, lingonberry, muntries, partridgeberry, and cultivars, varieties and/or hybrids of these

Pests and Application Rates:

Pests	Transform WG (oz/acre)
grape leafhopper mealybugs plant bugs	1.5 – 2.75 (0.047 – 0.086 lb ai/acre)
thrips (suppression only)	2.75 (0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest of small fruit vine climbing (except fuzzy kiwifruit) and within 1 day of harvest of low growing berry.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Strawberry

Pests and Application Rates:

Pests	Transform WG (oz/acre)
plant bugs	1.5 – 2.25 (0.047 – 0.071 lb ai/acre)
thrips (suppression only)	2.25 (0.071 lb ai/acre)

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.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

Soybean

Pests and Application Rates:

Pests	Transform WG (oz/acre)
soybean aphid	0.75 – 1.0 (0.023 – 0.031 lb ai/acre)
Suppression only: brown stink bug southern green stink bug	2.0 – 2.25 (0.063 – 0.071 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow

AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of grain, forage or hay harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- No more than two applications may be made to soybean forage.

Stone Fruits (Crop Group 12)[1]

[1]Stone fruits (crop group 12) including apricot, nectarine, peach, plum, prune, sweet cherry, tart cherry

Pests and Application Rates:

Pests	Transform WG (oz/acre)
aphids	0.75 – 1.5 (0.023 - 0.047 lb ai/acre)
San Jose scale (suppression only) western flower thrips (suppression only)	2.75 (0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for San Jose scale to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Succulent, Edible Podded and Dry Beans[1]

[1]Succulent, edible podded, and dry beans including adzuki bean, asparagus bean, bean, blackeyed pea, broad bean, chickpea, Chinese longbean, cowpea, fava bean, field bean, garbanzo bean, grain lupine, green lima bean, jackbean, kidney bean, lablab bean, lima bean, moth bean, mung bean, navy bean, pinto bean, rice bean, runner bean, snap bean, soybean (immature seed), sweet lupine, sword bean, tepary bean, wax bean, white lupine, white sweet lupine, yardlong bean

Pests and Application Rates:

Pests	Transform WG (oz/acre)
aphids	0.75 – 1.0 (0.023 – 0.031 lb ai/acre)

plant bugs	1.5 – 2.25 (0.047 – 0.071 lb ai/acre)
Suppression only: brown stink bug southern green stink bug	2.0 – 2.25 (0.063 – 0.071 lb ai/acre)
thrips (suppression only)	2.25 (0.071 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 14 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

Tree Nuts (Crop Group 14)[1] and Pistachio

[1]Tree nuts (crop group 14) including almonds, cashew, chestnut, filbert (hazelnut), macadamia nut, pecan, walnut

Pests and Application Rates:

Pests	Transform WG (oz/acre)
aphids	0.75 – 1.5 (0.023 - 0.047 lb ai/acre)
San Jose scale (suppression only)	2.75 (0.086 lb ai/acre)

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area. Time application for San Jose scale to the crawler stage.

Application Rate: Use a higher rate in the rate range for heavy pest populations.

Restrictions:
- **Preharvest Interval:** Do not apply within 7 days of harvest.
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than four applications per crop.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

Turfgrass

(For application only to commercial sod farms and grass grown for seed)

Pests and Application Rates:

	Transform WG

Pests	(oz/acre)
aphids (greenbug)	1.5 (0.047 lb ai/acre)
chinch bugs (suppression only)	2.75 (0.086 lb ai/acre)

Application Method: Dilute Transform WG in water and apply using suitable hand- or power-operated application equipment (such as tractor-mounted, portable pump-up, backpack, hydraulic, boom, turf "spray gun") in a manner to provide complete and uniform plant coverage.

Restrictions:
- **Minimum Treatment Interval:** Do not make applications less than 7 days apart.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.
- Do not feed treated grass cuttings (hay) or seed screenings to livestock or use hay for livestock bedding.
- Do not apply to golf courses, parks, playgrounds, athletic fields, or residential lawns.
- Do not make aerial applications to turfgrass.
- Do not apply this product at any time between 3 days prior to bloom and until after petal fall.

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February 10, 2013

Subject: Comments on the Conditional Registration of Sulfoxaflor

Docket Number: EPA-HQ OPP-2010-0889

Dear Sir/Madam,

My comments are based on my reading and interpretation of the supplemental information in light of my profession as a cotton farmer, private applicator and, commercial beekeeper. My commercial bee business earns 80% of its income from pollination of many of the crops listed under the proposed conditional registration. I earned a B.S. degree from the University of Arizona in biological studies in 1976. I worked at the Tucson Bee Laboratory while attending the University Of Arizona in the area of maintaining colonies in greenhouses testing bee diet studies and open field pollination studies.

I have participated in the PPDC pollinator work groups during 2012 to date. My comments will reflect the concerning discovers of those meetings and email exchanges as they pertain to this proposed registration.

A. Economic Assessment. 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.

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.

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!

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), 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.
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 substantuated 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.

I am very apprehensive of Sulfoxaflor being registered. I fear the severe damage to the declining pollinator population resulting from sunrise to sunset applications and extended residual toxicity in pollen and nectar. EPA should adequately reconsider the adverse effects that will occur to the present inadequate supply of managed pollinators and severely reduced population of native pollinators by Sulfoxaflor being used in the fashion I describe. The benefit does not balance the risk.

Thomas R. Smith
1031 S. Brahma Lane
Yuma, AZ 85364

National Pollinator Defense Fund
P.O. Box 193
Danbury, TX 77534
www.PollinatorDefense.org

February 12, 2013

OPP Docket
Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460

Re: Proposed Conditional Registration of Sulfoxaflor, Docket No. EPA-HQ-OPP-2010-0889

This letter is submitted on behalf of the National Pollinator Defense Fund, the American Honey Producers Association, the National Honey Bee Advisory Board, the American Beekeeping Federation, and the Russian Honeybee Breeders Association in regards to EPA's proposed conditional registration of sulfoxaflor. Our groups represent commercial beekeepers who both produce honey and provide pollination services, honey bee breeders, and hobby beekeepers.

We are writing to urge US EPA to deny the request for conditional registration of sulfoxaflor. The Agency does not have sufficient information to confirm that no unreasonable adverse effects will occur if this chemical is registered. In fact, the known characteristics of sulfoxaflor and the uses for which it is proposed suggest that it has the potential to have significant adverse impacts on pollinators. In the context of the current crisis in pollinator survival, the registration of yet another systemic insecticide with high acute toxicity and insufficient data regarding potential sublethal effects is ill-advised and does not meet the FIFRA standard of no unreasonable adverse effects.

The Economics of Pollination

As beekeepers, we are facing the worst season the industry has seen to date, with overwintering losses ranging from 30–90%, and averaging approximately 45%. For a representative beekeeper with 3,000 hives and a conservative estimate of income of $300/hive over the course of a year, a 45% loss represents $405,000. For the beekeeping industry as a whole, with 2.5 million hives, the loss is $337.5 million. Losses of this magnitude are not sustainable. While not all of the losses are due solely to pesticides, there are strong correlations between pesticide use and impaired colony performance (see below).

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 (Figure 1).

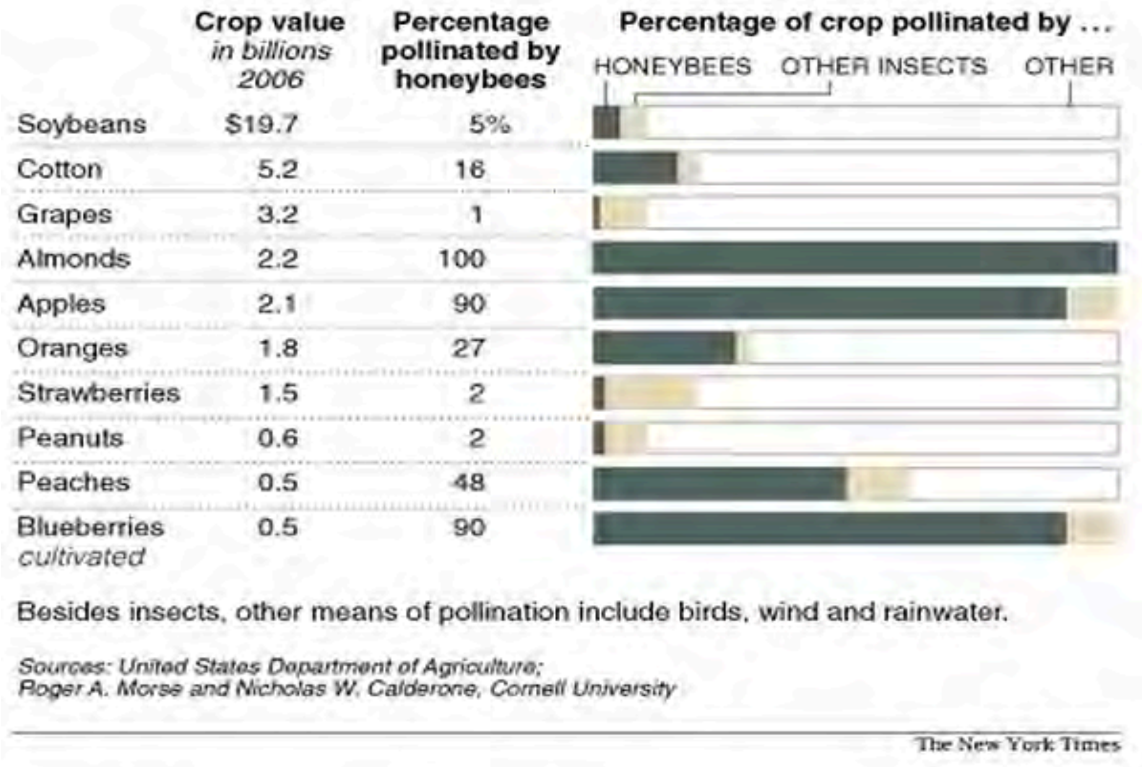

Figure 1: USDA estimates that pollination services account for $15B worth of crop value.

In 2011, RaboBank issued a report on the global decline of pollinators (appended to this letter for reference), flagging this issue as a major potential liability for agriculture if the steep decline in bee populations cannot be arrested.[1] The report notes:

> *Considering that this [the decline of bee populations] is a global issue and that the inherent economic impact of a further decline of bee colonies may be substantial, the tide must be turned. This will require increased cooperation between the academic world, governmental bodies, apiarists and companies directly dependent on pollination. The beekeepers, mostly loosely organised in apiarist associations, will not be able to solve the issue themselves.*

Any analysis of the economics of the costs and benefits associated with the conditional registration of a new pesticide with potential to cause both acute and sublethal poisoning of honey bees must account for the value of pollination services to the agricultural economy.

US EPA's Economic Analysis Needs a Reality Check

The US EPA Biological and Economic Analysis Division (BEAD) conducted an economic analysis of sulfoxaflor benefits for crop production and possible adverse impacts to honey bees, concluding:

[1] Rabobank. 2011. The Plight of the Honey Bee: Why the Loss of Honey Bee Colonies May Sting Global Agriculture. https://www.rabobank.com/nl/press/news/the_plight_of_the_honey_bee.html.

> *"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 times when flowers are not present or late afternoon sprays with reduced bee activity."*

BEAD has incorrectly assessed a number of issues in this analysis. We discuss these issues below.

1) Foraging behavior of bees

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[2] 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

[2] PRI, 2012. *Survey on Acute Pesticide-Related Bee Kills.* Pesticide Research Institute. http://www.pesticideresearch.com/site/?page_id=24.

facts correct in the interest of avoiding further losses. With the inadequate mitigations proposed in the BEAD analysis, future acute kills from sulfoxaflor applications are highly likely.

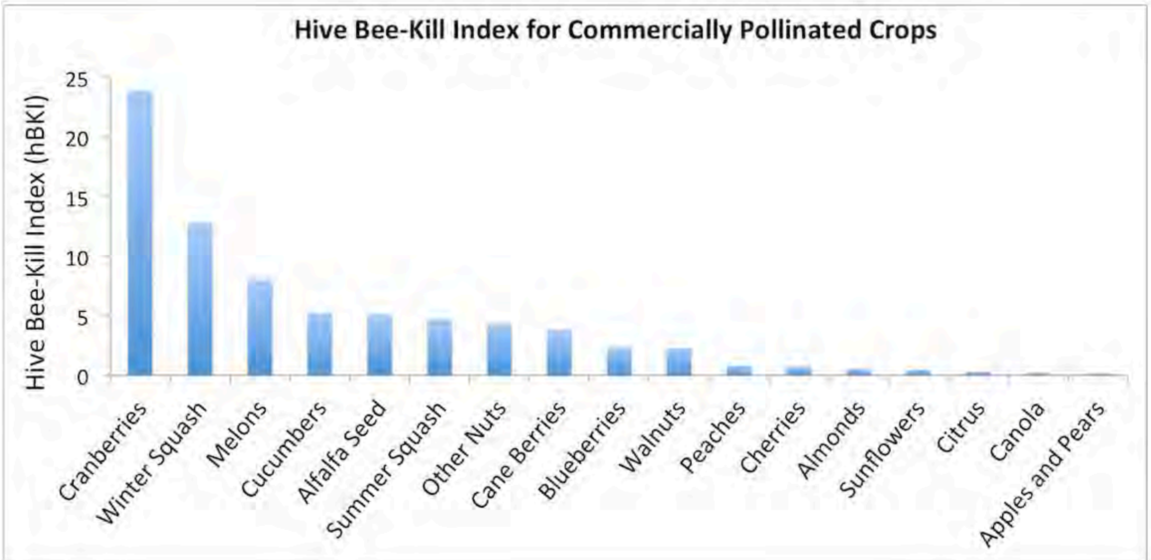

Figure 2: The hive bee-kill index is a measure of number of acute poisonings per acre of crop planted. For a detailed description of the index, see http://www.pesticideresearch.com/site/?page_id=2360/.

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 (Figure 3). 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.

Figure 2: This bee is covered with pollen after foraging in cotton and will carry it back to the hive.

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.

2) Potential long-term effects of exposure to sublethal levels of sulfoxaflor are unevaluated

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.

3) Commercial beekeeping is a migratory operation.

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.

The Role of Pesticides in Honey Bee Losses

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),[3] impaired immune function (making the bees more susceptible to pathogens),[4] disruption of hive communications (reducing the efficiency of the hive),[5] and decreased homing abilities that result in loss of foragers.[6]

The use of systemic insecticides has increased over time, as registered uses have expanded (see Figure 3). 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.

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[3] Tasei JN. 2001. Effects of insect growth regulators on honey bees and non-Apis bees. A review. *Apidologie* 32: 527–546.
[4] Desneux N, Decourtye A, Delpuech J-M. 2007. The sublethal effects of pesticides on beneficial arthropods. *Annu. Rev. Entomol*. 52:81-106.
[5] 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.
[6] Henry M, Béguin, M, Requier F *et al.* 2012. A common pesticide decreases foraging success and survival in honey bees. *Science* 336:348–350.

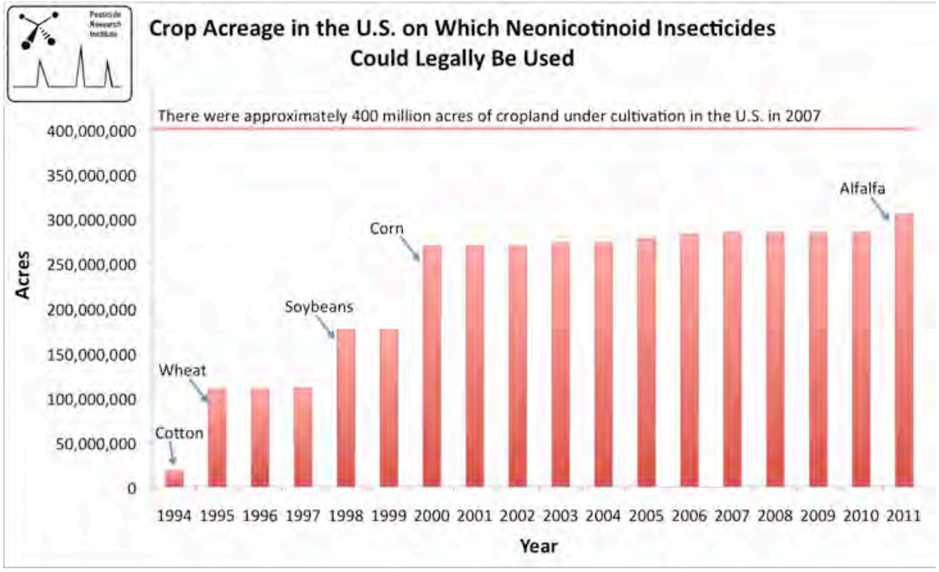


Figure 3: Acreage of crops on which neonicotinoid insecticides have been approved for use.

EPA Cannot Conclude That No Unreasonable Adverse Effects Will Occur

FIFRA requires a comprehensive set of studies on each pesticide prior to registration. For a Conditional registration, Section 3(7)(c) 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. Sulfoxaflor has the same constellation of properties as many of the other systemic insecticides that have been shown to cause acute and sublethal effects, including:

a) High acute toxicity to bees
b) Sufficient water solubility to permit systemic uptake by the plant and be expressed in pollen and nectar, as indicated by some of the studies already evaluated
c) Sufficient persistence in the environment that would permit pollinator exposures through drinking runoff from treated areas and from ingestion of nectar and pollen from treated plants.

The absence of valid protocols for field tests precludes a comprehensive understanding of the potential for long-term and/or sublethal effects of sulfoxaflor on colony health. We await the Pellston report on this topic for further guidance, but in the interim, there is insufficient information to conclusively determine that no unreasonable adverse effects will occur, and many warning flags that suggest that unreasonable adverse effects are unavoidable.

The existing field studies for sulfoxaflor are flawed, as EPA reviewers noted. For example, having a control hive that is infected with varroa will not provide a relevant or useful comparison (MRID48445806). The studies also failed to evaluate representative label application rates and did not evaluate colony health and survival after the short-term studies were completed. In effect, EPA has no reliable information on the long-term effects of sulfoxaflor. Until validated study protocols are in place to test the long-term/sub-lethal effects of sulfoxaflor, US EPA cannot definitively determine that no unreasonable adverse effects will occur.

Without a Viable Incident Reporting System, EPA Cannot Track the Impact of Conditional Registration Decisions

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.

Pollinator Protection Requires Meaningful Enforcement Efforts

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.

Conclusion

For decades, the bee industry has absorbed slight losses from pesticides as a cost of doing business; however this year’s current projected loss of $337.5 million has put us in a position of having to absorb an unreasonable amount of damage. The situation requires an immediate correction from EPA to ensure the survival of commercial pollination services, native pollinators, and the plentiful supply of fruits, vegetables, and nuts that pollinators make possible. US EPA must eliminate the potential for unreasonable adverse effects on our livestock and livelihoods and the nation’s food supply, as mandated under FIFRA. The best way to ensure no unreasonable adverse effects from sulfoxaflor is to refuse to grant a conditional registration until all of the data are in, and only grant the full registration if the data indicate that this pesticide can be used without damaging our livestock. We strongly urge EPA to take this path.

Sincerely yours,

Bret Adee, President
National Pollinator Defense Fund

Randy Verhoek, President
American Honey Producers Association

George Hansen, President
American Beekeeping Federation

Dave Hackenberg, Co-Chair
Bret Adee, Co-Chair
National Honey Bee Advisory Board

Steven Coy
Russian Honey Bee Breeders Association

The Plight of the Honey Bee

Why the Loss of Honey Bee Colonies May Sting Global Agriculture

Contents

The recent steep increase in honey bee colony losses mainly in Europe and the United States has drawn much attention. There are reasons for concern. Approximately one-third of global food production is to some extent dependent on animal pollination, mainly by the honey bee. This dependence is growing as the production of pollination-requiring crops is increasing rapidly and the role of wild pollinators is shrinking.

Introduction

A steep increase in honey bee colony losses has been reported around the globe in recent years. In the United States (US), a phenomenon called 'colony collapse disorder' — first discovered in 2006 — has caused inexplicable losses. The rate of bee colonies not surviving the winter ranged between 30 percent and 35 percent on average for the years 2006/2007 to 2009/2010 — a loss rate of 10 percent would be considered normal. However, some of the worst-hit beekeepers have reported losses of up to 90 percent. Most countries in Europe have also been experiencing colony losses above 20 percent in the past few years. What exactly is causing the increased colony losses remains subject to further investigation. However, the academic world now seems to agree that rather than one factor there is a mixture of potentially synergistic causes for the losses. Although problems have been the worst in Europe and the US, inexplicable losses are also being witnessed in Asia, South America and the Middle East.

This increase in bee colony losses has drawn much attention from the media, politicians, the academic world and the general public. Some even paint apocalyptic scenarios whereby mankind could vanish along with the honey bee. But this is unlikely, as some of the major staple crops like rice, wheat and corn do not require animal pollination. Also, high bee colony losses are not entirely new: in the early 20th century, an epidemic known as the Isle of Wight disease wiped out nearly all the bees from the British Isles.

Nevertheless, there is some reason for concern. A further decline in honey bee numbers could cause a pollination shortage and subsequently impact yields of pollination-dependent crops like apples, pears and cocoa. In a more extreme scenario, farmers might not be able to grow some crops profitably. Furthermore, the issue — which is now global rather than local — is compounded by world agriculture's increasing dependence on the honey bee.

Agriculture Becoming Increasingly Dependent on Bee Pollination

Some 90 agricultural crops, representing one-third of global food production volume, are to some extent dependent on animal pollination. The total value is even higher as pollination-dependent crops — like apples, blueberries and coffee — tend to be more valuable than wind-pollinated crops like wheat, rice and corn. There are several pollinating animal species, but the domesticated honey bee is by far the most important one, accounting for an average of 80 percent to 90 percent of total animal pollination.

The impact of pollination varies by crop. For some crops, like almonds or melons, pollination is absolutely essential as poor pollination would cause a failed harvest. For other crops, such as oranges and grapefruit, pollination has a small but valuable impact on the size and quality of the fruit.

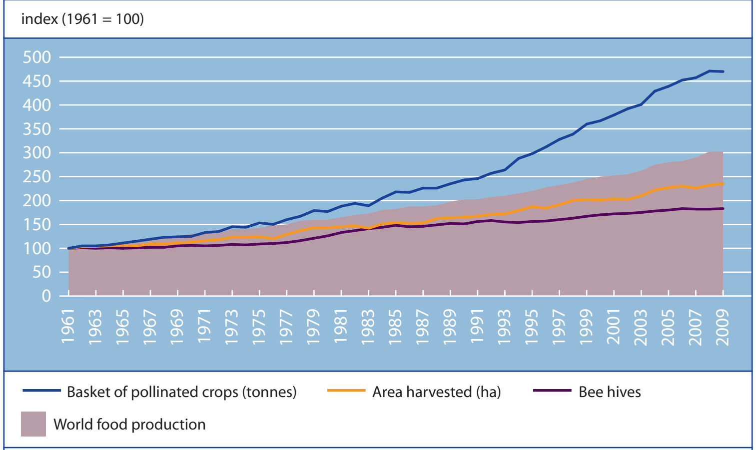
In the past 50 years, global production of pollination-dependent crops has grown at an accelerated pace relative to the overall growth in food production. In the past five decades, world food production tripled while the production of our reference basket of pollination-dependent crops[1] nearly quintupled (*see Figure 1*).

In other words: pollination-dependent crops represent a larger proportion of the average diet than they did 50 years ago. This is because rising disposable incomes have encouraged consumers to include more fresh fruits and vegetables in their

[1] According to Alexandra Klein et alia (2006) 87 of the leading global food crops are dependent on animal pollination. We have included the production volumes per country of those crops for which sufficient data for the period 1961-2009 was available. This has resulted in a basket of 35 leading crops with a varying number of countries per crop, depending on the availability of data. The aggregate production volume has been indexed with 1961 as the base year. Crops included are: almond, apple, apricots, avocados, aubergine/eggplant, blueberry, broad bean, buckwheat, cantaloupe/melon, cashew nut, cherry, chilli, cocoa, coconut, coffee, cotton, cow pea, cranberry, cucumber, grapefruit, lemon, mango, okra, orange, papaya, peach/nectarine, pear, plum/sloe, pumpkin, rapeseed, raspberry, soybean, sunflower seed, tomato, watermelon.

PER 000332

Figure 1: Global Production of Pollination-dependent Crops vs. Global Managed Bee Colonies



Source: FAOSTAT, 2010

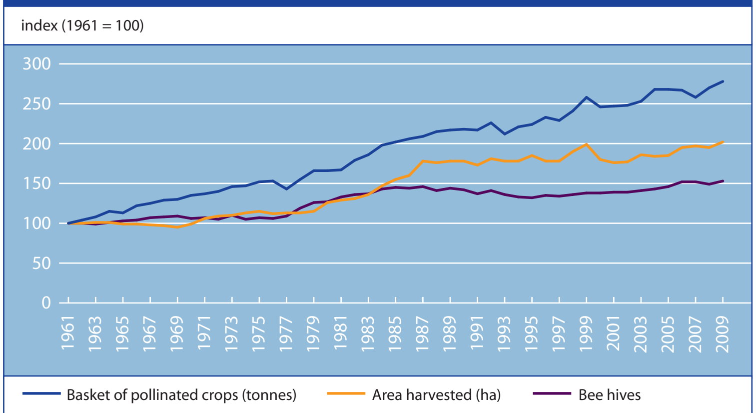
[2] Research by Marcelo A. Aizen and Lawrence D. Harder (2009) has also shown that the global stock of domesticated honey bees is growing slower than agricultural demand for pollination.

diets. This trend is expected to continue on the back of rising income levels in emerging giants like China and Brazil, as people continue to diversify their diets and move away from major staple crops like corn, wheat and rice, which do not require animal pollination.

Production Growing Faster Than the Number of Managed Bee Hives

Although the global stock of managed bee colonies may be growing, the demand for agricultural pollination is increasing more rapidly[2]. This is illustrated by our estimate that in the past 50 years the global acreage planted with pollination-dependent crops has increased by 135 percent while the number of managed bee colonies grew by 83 percent. In Europe, among the regions with the highest colony-loss rates, the gap has grown even wider as the acreage requiring pollination doubled while the number of bee colonies only grew by some 50 percent. (*see Figure 2*).

Figure 2: Production vs. Available Bee Colonies in Europe



Source: FAOSTAT, 2010

However, the US has been identified as a key risk region, as the situation there is much more extreme (*see Figure 3*). Production of pollinated crops has quadrupled since 1961 whereas the number of managed bee colonies has more than halved. The latter development has been driven by cheap honey imports from Asia and beekeeping being an ageing profession. The consequence is that the average number of bee colonies per pollination-requiring hectare has declined by nearly 90 percent. This does not suggest a causality between the decline in bee colonies relative to the demand for agricultural pollination and the colony losses observed in recent years; rather, this development illustrates the growing, inherent risk of colony losses as the average colony is responsible for a greater pollination task.

On the other hand, farmers have managed to grow produce with relatively fewer bee colonies up to this point, and there has been no evidence of agricultural yields being affected by a decline in pollinators. But the question is how much further this situation can be stretched. In the US, there have already been situations in which bee colonies have been imported from Australia to cover a pollination shortage due to high mortality rates of domestic colonies.

Role of Managed Bee Hives More Important Relative to Wild Pollinators

In addition to the growth in food production volumes, another reason global agriculture is becoming increasingly dependent on the honey bee is that production methods have changed greatly in the past century. The total global agricultural acreage has not grown nearly as fast as total production. This is because of the yield improvements that are enabled by the enormous technological advances made in agriculture during the second half of the 20th century.

Part of the advancement in improving agricultural yields is due to the fact that crops are increasingly grown under monoculture. This is also the case for pollination-dependent crops. This has had a double-edged effect on agriculture's dependence on managed bee colonies. First, the acreage requiring pollination has simply increased, and second, areas under monoculture often require bringing managed bee hives to the field, as areas under monoculture do not usually provide the right living conditions to host wild pollinators that would normally be found in areas with greater biodiversity. Even if a crop field is surrounded by forest, wild pollinators only reach the borders of the field, as their radius is usually much smaller than that of the honey bee, which can cover an area of up to seven kilometres around the hive.

So What's Causing Colony Deaths?

The exact cause for the rapid rate of bee colony losses witnessed in recent years remains unclear. A lot of scientific research has been conducted to uncover the culprit, often leading to contradictory conclusions. But the academic world now seems to agree that there is no single cause to this issue; it is more than likely that a number of causes have together formed a lethal cocktail. Some of the causes may even have synergistic effects, but exactly how they interact is currently subject to investigation.

Honey bees used for human purposes are bred to be friendly, efficient in pollination and able to produce large amounts of honey. This is what could be called commercial selection over natural selection. Bee queens, the only bees in a hive that produce larvae, are bred by a relatively small number of commercial breeders. This inbreeding has caused a huge decline in diversity and thereby a shrinking gene pool, which in turn has affected the specie's resilience to adverse influences or natural enemies. The best known example is the varroa destructor, a parasitic mite that weakens the bee.

The wider decline in biodiversity also has its effect on the honey bee. Increased monoculture and the coinciding loss of semi-natural habitat have impacted the bees' diet; the lack of variation has led to malnutrition of managed bee colonies. For the same reason, wild pollinators including wild bees are suffering in many regions.

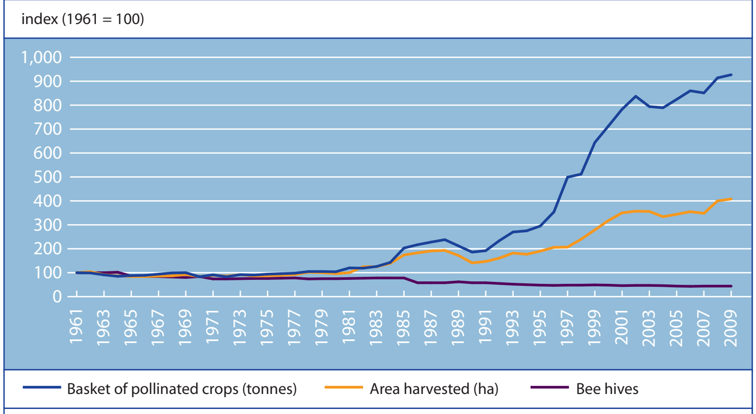
Another suspected cause is pesticide use. This has led to bans on certain pesticides linked to bee colony losses in France and Germany. There seems to be no agreement among stakeholders about the exact role of pesticides; they are the major cause according to some, and are considered less relevant by others. Yet, in Sichuan (Southern China) the application of too much pesticide during the 1980s wiped out many insects, including bees. Therefore, each spring, pollination in this area is carried out by hand, an enormously labour-intensive task considering that a single bee colony can pollinate up to 300 million flowers a day.

Outlook

Most of the suspected factors causing bee colony losses are linked to modern agriculture. At the same time, modern agriculture has provided the world with great benefits. Today, 1.5 times more food per capita is produced than was produced 50 years ago and this food is of greater quality and greater diversity than half a century ago.

The achievements of modern agriculture must be maintained. As world population continues to grow, so too will the demand for food. Additionally, the demand for pollination-dependent crops is expected to continue to grow faster than world food production, as the global average disposable income continues to rise. To service that demand, sustainable methods for maintaining animal pollination services — which already support 35 percent of global food production — must be developed.

Figure 3: Production vs. Total US Bee Colonies



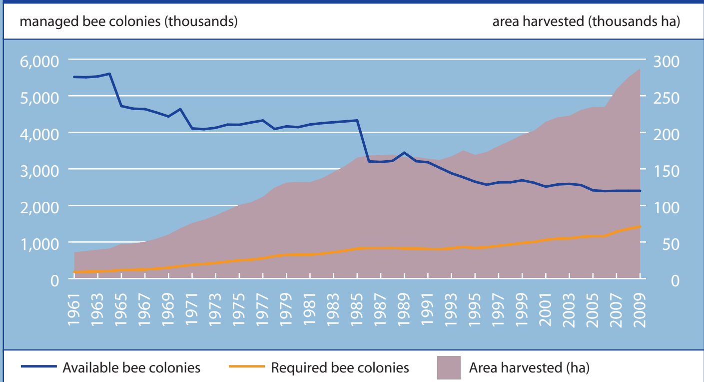
Source: FAOSTAT, 2010

Box 1: The Californian Almond Industry

Probably the most remarkable example of the relation between the intensification of agriculture and the dependence on the honey bee is the US almond industry in California's Central Valley. In the past 50 years, the industry has grown eightfold in terms of cultivated area and nearly twentyfold in terms of production. Now, with a total of over 275,000 hectares and more than 60 million trees, the area accounts for more than half of global almond production.

While the almond industry grew impressively throughout the past decades, the number of managed bee colonies in the US more than halved. Thus, the number of available managed bee colonies and the number of colonies required to pollinate the crop have been converging (*see Figure 4*). The further the number of available colonies and the number of required colonies converge, the greater the risk that future colony losses will have an economic impact on the almond industry. How and when the high colony losses will stop remains unclear, but the total acreage of US almond crops continues to grow.

Figure 4: Almond Production and Bee Colony Convergence



Source: FAOSTAT, 2010

Considering that this is a global issue and that the inherent economic impact of a further decline of bee colonies may be substantial, the tide must be turned. This will require increased cooperation between the academic world, governmental bodies, apiarists and companies directly dependent on pollination. The beekeepers, mostly loosely organised in apiarist associations, will not be able to solve the issue themselves.

First, a better understanding of how the suspected causes of colony losses interact and how bees respond to those causes is needed. This will require coordinated research and more close and consistent monitoring of bee colonies, as sufficient quality data is often lacking.

In the mean time, to save the genetic diversity currently present among the bees, breeding projects should be developed, with or without governmental support. Furthermore, biodiversity in agricultural areas should be increased to provide greater nutritional variety for the bees pollinating the crops, and to promote the right living conditions for attracting wild pollinating species that could take over part of the pollination job. A practical solution would be introducing a variety of plants between permanent crops or promoting weedy borders.

In addition, although the use of pesticides cannot always be avoided, application should take place in cooperation with beekeepers. A simple but effective measure is avoiding pesticide use during daylight hours, when bees are foraging.

For those producing pollination-dependent crops, one thing is clear: pollination should not be considered as a production factor to be taken for granted going forward.

Food & Agribusiness Research and Advisory
Author: Ruben Verwijs
Telephone: +31 30 71 22096
E-mail: Ruben.Verwijs@rabobank.com

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Insect Pollinated Crops, Insect Pollinators and US Agriculture: Trend Analysis of Aggregate Data for the Period 1992–2009

Nicholas W. Calderone*

Department of Entomology, Cornell University, Ithaca, New York, United States of America

Abstract

In the US, the cultivated area (hectares) and production (tonnes) of crops that require or benefit from insect pollination (directly dependent crops: apples, almonds, blueberries, cucurbits, etc.) increased from 1992, the first year in this study, through 1999 and continued near those levels through 2009; aggregate yield (tonnes/hectare) remained unchanged. The value of directly dependent crops attributed to all insect pollination (2009 USD) decreased from $14.29 billion in 1996, the first year for value data in this study, to $10.69 billion in 2001, but increased thereafter, reaching $15.12 billion by 2009. The values attributed to honey bees and non-*Apis* pollinators followed similar patterns, reaching $11.68 billion and $3.44 billion, respectively, by 2009. The cultivated area of crops grown from seeds resulting from insect pollination (indirectly dependent crops: legume hays, carrots, onions, etc.) was stable from 1992 through 1999, but has since declined. Production of those crops also declined, albeit not as rapidly as the decline in cultivated area; this asymmetry was due to increases in aggregate yield. The value of indirectly dependent crops attributed to insect pollination declined from $15.45 billion in 1996 to $12.00 billion in 2004, but has since trended upward. The value of indirectly dependent crops attributed to honey bees and non-*Apis* pollinators, exclusive of alfalfa leafcutter bees, has declined since 1996 to $5.39 billion and $1.15 billion, respectively in 2009. The value of alfalfa hay attributed to alfalfa leafcutter bees ranged between $4.99 and $7.04 billion. Trend analysis demonstrates that US producers have a continued and significant need for insect pollinators and that a diminution in managed or wild pollinator populations could seriously threaten the continued production of insect pollinated crops and crops grown from seeds resulting from insect pollination.

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* E-mail: nwc4@cornell.edu

Introduction

Flowering plants (Angiosperms) play critical roles in many natural and agricultural ecosystems, providing food, fiber and shelter for wildlife and humankind alike [1]. In humans, high levels of fruit and vegetable consumption are associated with decreased risk of chronic disease [2–5]. Additionally, there is growing interest in the use of plants as fuel sources [6–11]. Pollination is an essential step in the reproductive process of the world's nearly 300,000 species of flowering plants because it is usually required for the production of seeds [1,12–17]. Pollination is the transfer of pollen, bearing the male gamete, from the anther of a flower to the stigma of a flower. After landing on a receptive stigma, a pollen grain germinates and a pollen tube develops, growing through the supporting style to the ovary. Genetic material in the pollen grain travels through the pollen tube to the ovary where it unites with an egg, the female gamete, in a process called fertilization. The fertilized egg develops into a seed, and that process is often accompanied by the development of fruit from surrounding tissue [18]. Depending on the species, from one to several hundred eggs must be fertilized to ensure a high quality fruit because each egg requires a separate pollen grain for fertilization. Plants with incompletely pollinated flowers have fewer seeds and reduced fitness, and they produce inferior fruit with reduced market value [19,20].

Pollination can result from the action of abiotic forces such as wind and water, but 80% of the Angiosperms rely on animals, including bats, flies, butterflies, beetles and other insects [1]. The majority of pollinators are insects, and the majority of those are bees (*Anthophila*) [13], of which there are approximately 17,000 described species and as many as 30,000 species worldwide [1,21]. With rare exception, bees collect pollen and nectar from flowers for food, transferring pollen in the process. North America is home to nearly 4,500 species of bees [21]. Most are solitary, but there are 49 known species of the primitively eusocial bumble bee in the US, 41 of which are also found in Canada; an additional 11 species are found in Mexico. The highly eusocial western honey bee, *Apis mellifera*, was introduced to North America from Europe and Africa beginning in 1622 [22,23]. It is the only species of honey bee in North America.

Recent events affecting the health of honey bees and other insect pollinators [1], both in the US and abroad, have renewed interest in the pollination services they provide in both natural and agricultural ecosystems [14,24–28]. This concern is driven, in part,

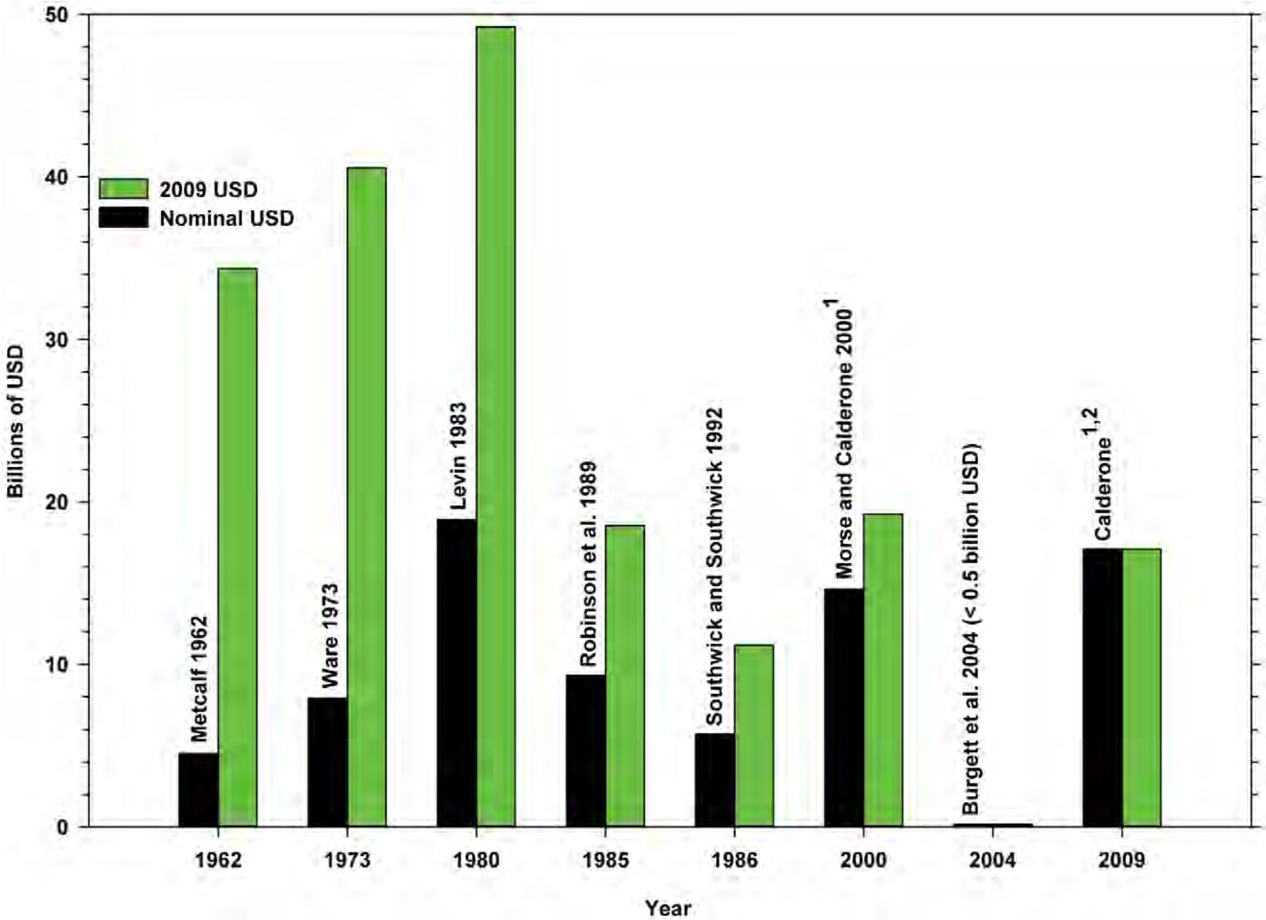

Figure 1. Historical estimates of the value of honey bees to US agriculture. [1]Includes both directly dependent crops (apples, almonds, cherries, oranges, squash, vegetable and legume seeds, etc.) and indirectly dependent crops (field crops and vegetables); [2]present study.
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Table 1. General farm and US population data.

Year	US Population[1]	THIF[1,2]	Cropland value (nominal USD per hectare)	Cropland value (2009 USD per hectare)
1992	256.51	395.99	na	na
1993	259.92	392.08	na	na
1994	263.13	390.90	na	na
1995	266.28	389.52	na	na
1996	269.39	387.96	na	na
1997	272.65	386.88	3,138.24	4,194.81
1998	275.85	385.29	3,311.21	4,358.15
1999	279.04	383.83	3,484.19	4,486.72
2000	282.17	382.46	3,607.74	4,494.72
2001	285.08	381.24	3,731.29	4,520.05
2002	287.80	380.53	3,928.98	4,685.44
2003	290.33	379.09	4,101.95	4,782.72
2004	293.05	377.27	4,373.77	4,967.36
2005	295.75	375.52	5,090.37	5,591.77
2006	298.59	374.65	5,683.42	6,048.13
2007	301.58	372.90	6,251.77	6,468.70
2008	304.37	372.27	6,820.11	6,795.84
2009	307.01	372.23	6,597.71	6,597.71

[1]millions;
[2]hectares; THIF = total hectares in farms; na = not available.
doi:10.1371/journal.pone.0037235.t001

Table 2. Hectares of Directly and Indirectly Dependent Crops.

Year	HDD[1,2]	HDD as % THIF[4]	HDD crops per person	HID as % THIF[4]	HID[1,3]	HID crops per person	US Population[1]
1992	26.65	6.73	0.1039	3.80	15.03	0.0586	256.51
1993	26.52	6.76	0.1020	4.07	15.96	0.0614	259.92
1994	28.38	7.26	0.1079	4.09	15.98	0.0607	263.13
1995	28.68	7.36	0.1077	4.41	17.16	0.0645	266.28
1996	28.99	7.47	0.1076	4.07	15.79	0.0586	269.39
1997	31.60	8.17	0.1159	4.08	15.77	0.0578	272.65
1998	32.63	8.47	0.1183	3.81	14.69	0.0532	275.85
1999	33.42	8.71	0.1198	4.18	16.03	0.0574	279.04
2000	33.26	8.70	0.1179	4.07	15.57	0.0552	282.17
2001	33.45	8.77	0.1173	4.20	16.02	0.0562	285.08
2002	32.97	8.67	0.1146	3.96	15.07	0.0523	287.80
2003	32.89	8.68	0.1133	3.99	15.13	0.0521	290.33
2004	33.21	8.80	0.1133	3.92	14.80	0.0505	293.05
2005	32.66	8.70	0.1104	4.09	15.34	0.0519	295.75
2006	33.44	8.92	0.1120	3.85	14.44	0.0483	298.59
2007	29.34	7.87	0.0973	3.62	13.50	0.0448	301.58
2008	33.81	9.08	0.1111	3.28	12.21	0.0401	304.37
2009	34.11	9.16	0.1111	3.32	12.35	0.0402	307.01

[1]millions;
[2]HDD = hectares directly dependent crops;
[3]HID = hectares indirectly dependent crops;
[4]THIF = total hectares in farms.
doi:10.1371/journal.pone.0037235.t002

Table 3. Production of Directly and Indirectly Dependent Crops.

Year	Tonnes DD crops[1]	Tonnes DD crops per person	Tonnes ID crops[1]	Tonnes ID crops per person	US Population[1]
1992	98.9255	0.4251	107.6731	0.4627	256.51
1993	92.0909	0.3906	106.3243	0.4509	259.92
1994	112.7269	0.4722	113.8044	0.4768	263.13
1995	102.1451	0.4228	112.4924	0.4657	266.28
1996	107.7844	0.4410	107.0707	0.4381	269.39
1997	119.8173	0.4844	109.8278	0.4440	272.65
1998	119.9575	0.4793	113.6954	0.4543	275.85
1999	114.9755	0.4542	117.9397	0.4659	279.04
2000	121.9736	0.4765	114.4079	0.4469	282.17
2001	124.3230	0.4807	107.5862	0.4160	285.08
2002	118.8422	0.4552	101.8749	0.3902	287.80
2003	110.3651	0.4190	107.9457	0.4098	290.33
2004	130.5823	0.4912	108.1939	0.4070	293.05
2005	127.0099	0.4734	105.7034	0.3940	295.75
2006	127.2814	0.4699	106.4888	0.3931	298.59
2007	112.2107	0.4101	103.6566	0.3789	301.58
2008	121.8626	0.4413	97.3146	0.3524	304.37
2009	130.3399	0.4680	100.7376	0.3617	307.01

[1]millions; DD = directly dependent crops; ID = indirectly dependent crops.
doi:10.1371/journal.pone.0037235.t003

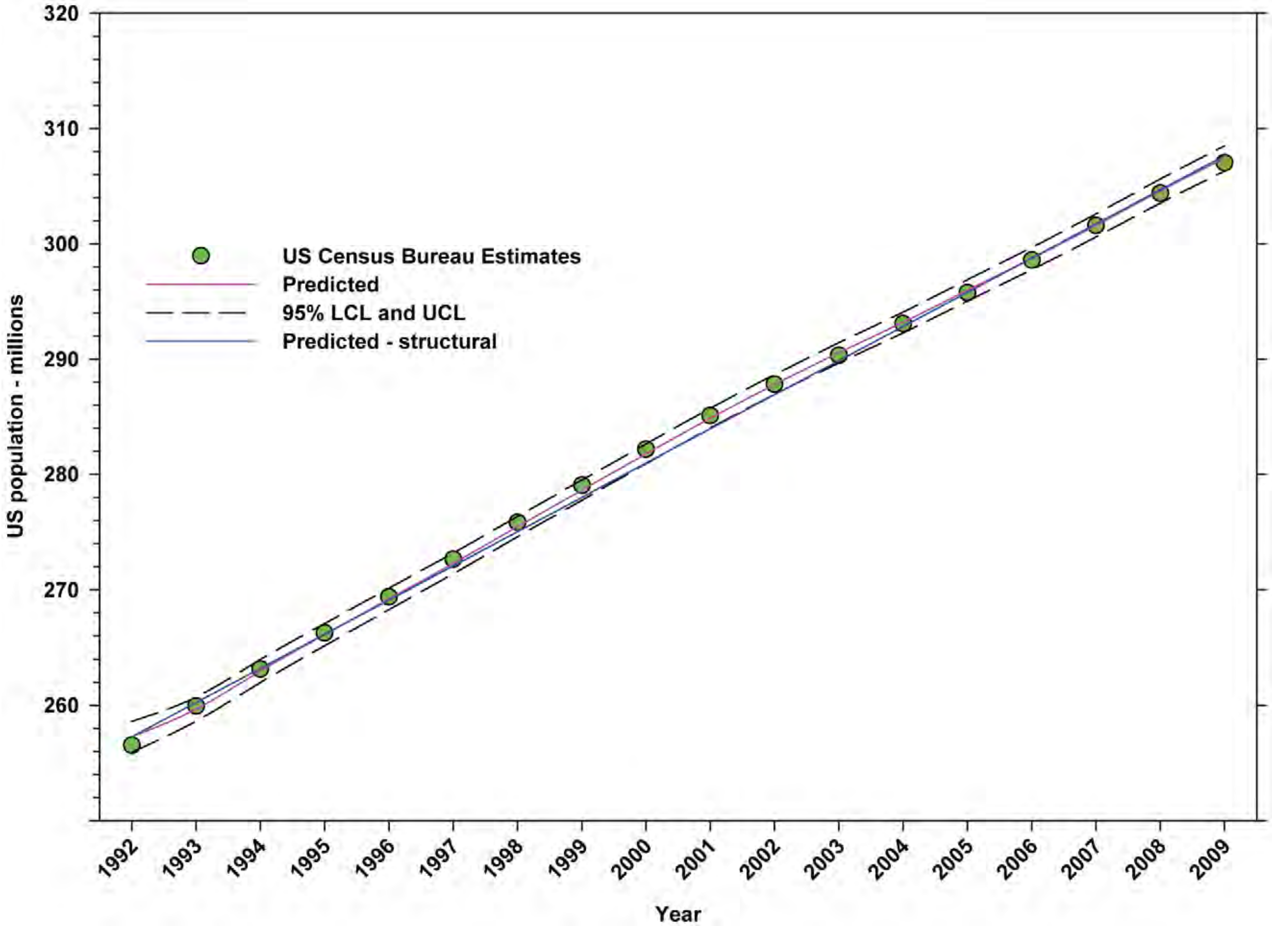

Figure 2. Estimates for the US population. Predicted values (pink) include adjustments for serial autocorrelation. Predicted – structural values (blue) are based solely on the structural elements of the model.
doi:10.1371/journal.pone.0037235.g002

Table 4. Results of the analyses of farm data in Table 1.

Variable	*y*-intercept	B_1x	B_2x^2
US population[1]			
Estimate ± SE	257.2553±0.4119	2.9637±0.0375	na
t	624.52	79.06	na
$P>\|t\|$	<0.0001	<0.0001	na
Total R^2	0.9997	na	na
Number of hectares in farms[1]			
Estimate ± SE	393.5825±0.2048	−1.3633±0.0197	na
t	1921.86	−69.31	na
$P>\|t\|$	<0.0001	<0.0001	na
Total R^2	0.9900	na	na
Value of cropland per hectare (2009 USD)			
Estimate ± SE	4,251±424.8061	14.2960±118.9520	17.7343±7.8747
t	10.01	0.12	2.25
$P>\|t\|$	<0.0001	0.9043	0.0243
Total R^2	0.9534	na	na

[1]millions; x = year; na = not applicable; *df* = 1 all effects.
doi:10.1371/journal.pone.0037235.t004

by data showing that the global cultivation of pollinator-dependent crops is increasing [29–31] while certain populations of native and managed pollinator species are declining or at risk [1,32,33]. Threats to native pollinator populations include agricultural intensification, habitat alteration and fragmentation, exotic pathogens, nutritional stress, pesticides and the loss of genetic variability, the latter being especially significant for the haplodiploid bees [25,34–47]; however, the impact of anthropogenic disturbances on bee abundance and species richness has not been well documented on a global level [48]. Additionally, the nature of the impact of declining pollinator populations is controversial. Crops that provide the majority of global calories do not require pollination [49,50] while those that provide other nutrients do require pollination [51].

Globally, the population of managed honey bees is increasing, albeit not at a rate that matches the global growth in the production of pollinator-dependent crops [30]; however, that growth is not shared by managed honey bees in the US [52]. Although the US honey bee population has a history of occasional precipitous, short-term losses [53], there has been a gradual, sustained decline since the peak of 5.9 million colonies in 1947 [52]. The number of managed colonies in the US reached a low of 2.3 million in 2008, although there were increases in 2009 and 2010 (methods for estimating colony numbers are discussed elsewhere [54]).

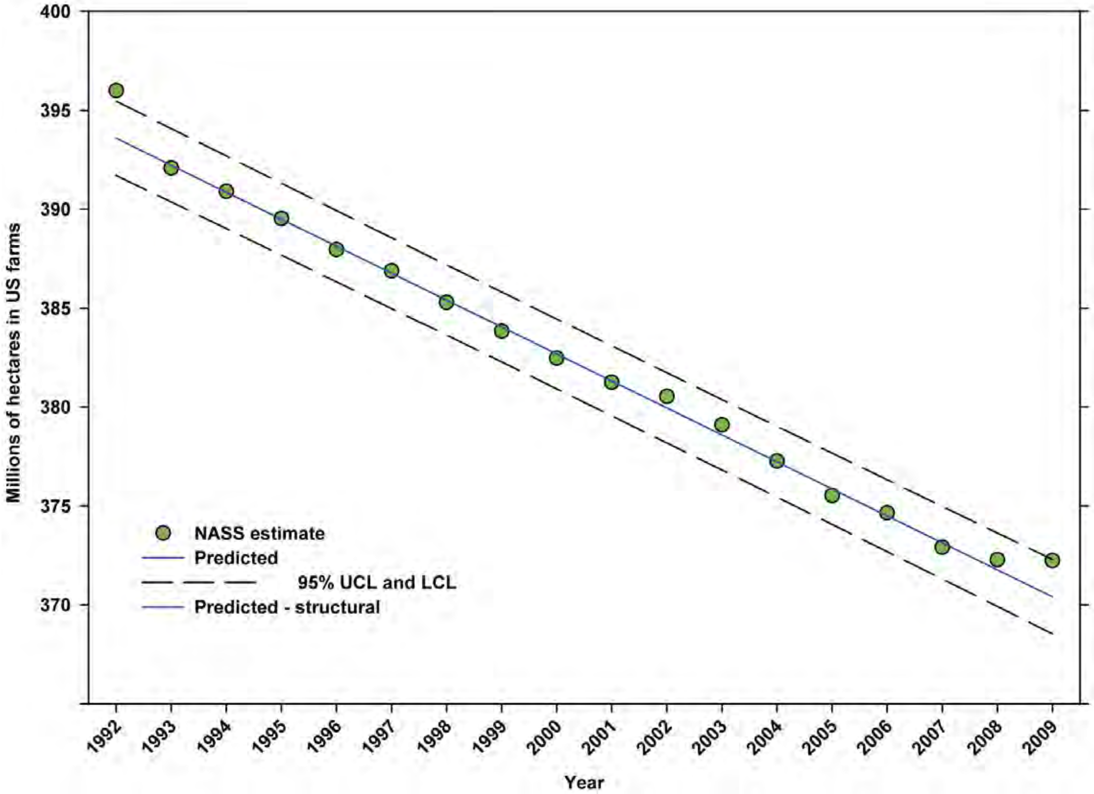

Figure 3. Total hectares in farms in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model.
doi:10.1371/journal.pone.0037235.g003

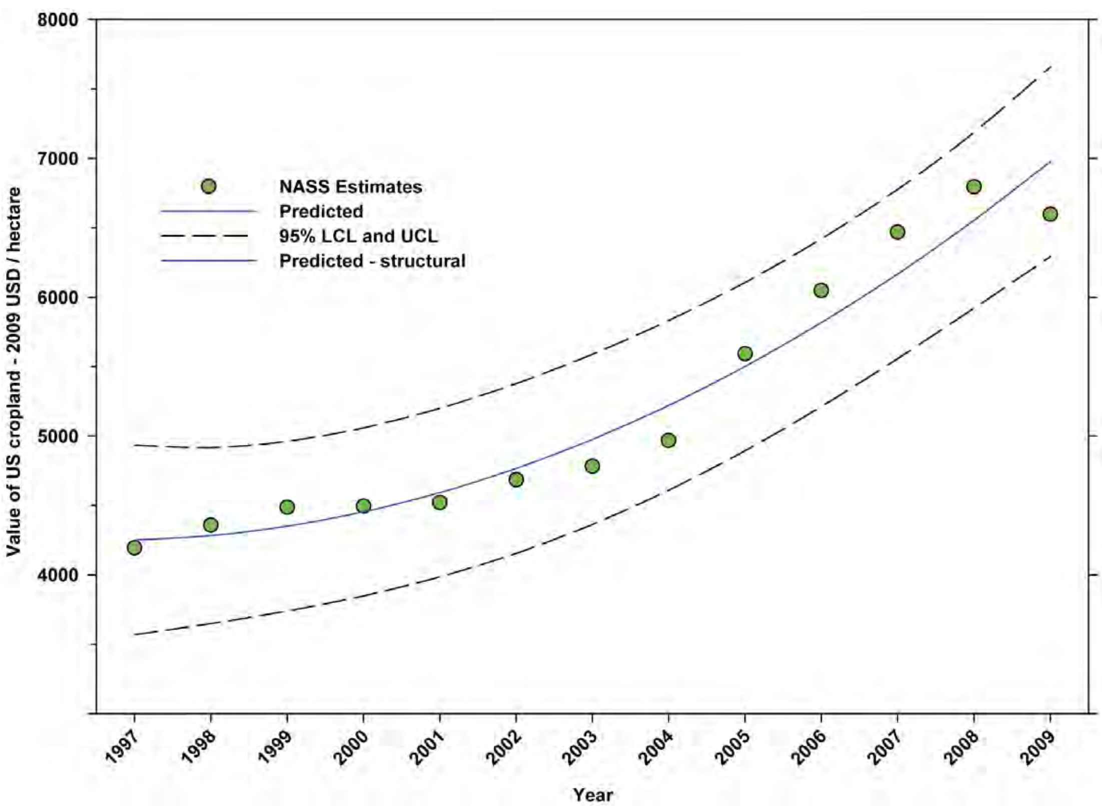

Figure 4. Value of cropland (2009 USD/hectare) in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model.
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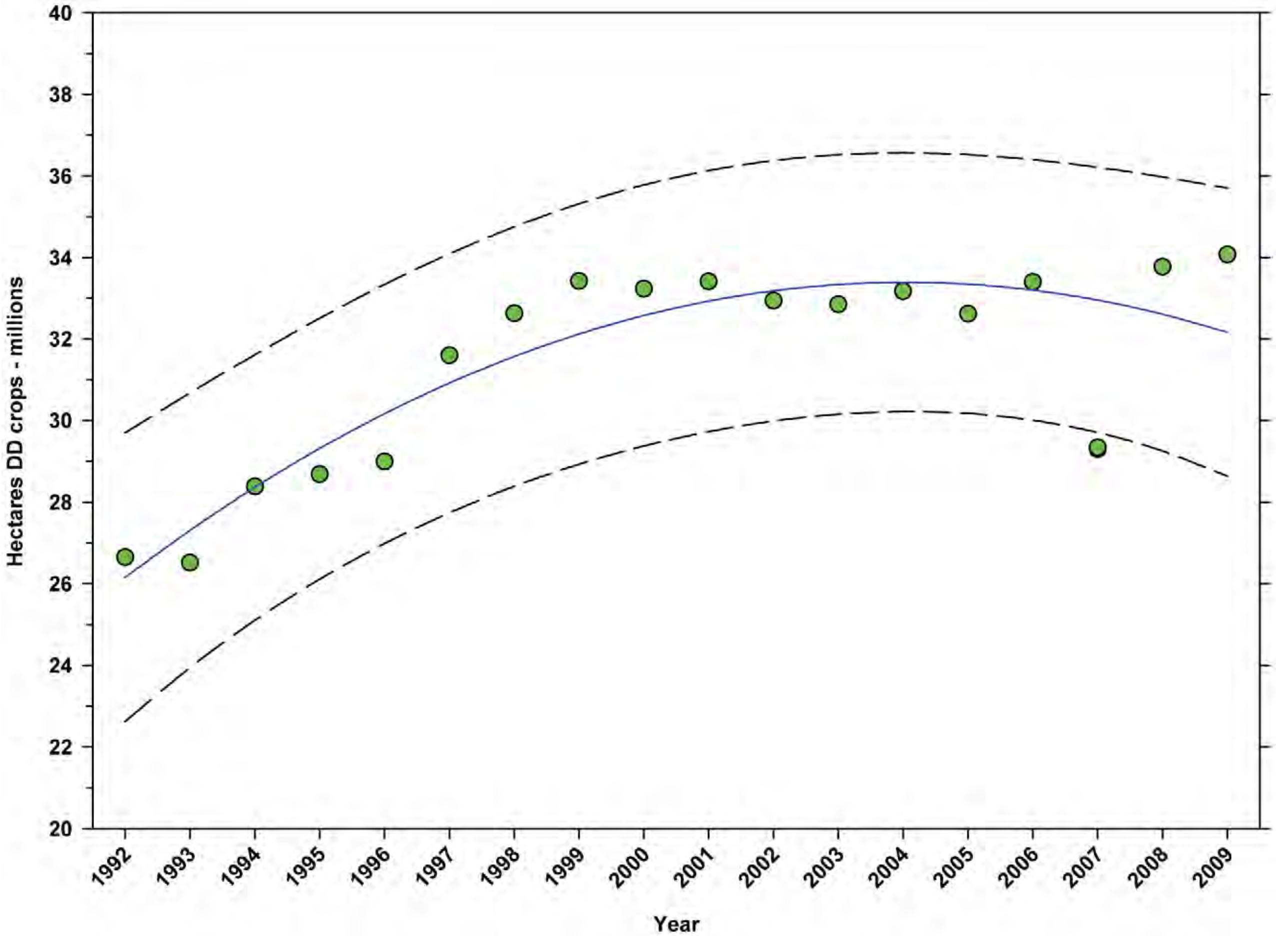

Figure 5. Number of hectares of directly dependent crops in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g005

Because honey bees and other insects play a pivotal role in many agricultural cropping systems, several estimates of the value they contribute to US agriculture have been published (Fig. 1; billion = B): $4.5 B in 1957 [55] (Metcalf), $7.9 B in 1972 [56] (Ware), $18.9 B in 1980 [57] (Levin), $1.6–5.7 B in 1986 [58] (Southwick and Southwick), $9.3 B in 1985 [59,60] (Robinson, Nowogrodzki, Morse), $14.6 B in 1996–1998 [61] (Morse and Calderone) and $150 million in 2004 [62] (Burgett, Rucker and Thurman). Inflation adjusted equivalents (2009 USD) are $34.36 B (Metcalf), $40.55 B (Ware), $49.21 B (Levin), $3.13 B–$11.16 B (Southwick and Southwick), $18.54 B (Robinson, Nowogrodzki, Morse), $19.22 B (Morse and Calderone) and $170.36 million (Burgett, Rucker and Thurman). The annual value of native pollinators for the period 2001–2003 is estimated at $3.07 B (~$3.66 B 2009 USD) [63] (Losey and Vaughan).

The variation in the above estimates can be attributed to the different approaches taken by the various authors. Metcalf [55] reported the total gross value of a group of 30 insect pollinated crops deemed to depend 'almost exclusively' upon insects for production but did not differentiate among the contributions of honey bees, non-*Apis* bees and other insects. Levin [57] included the total gross value of crops that require or benefit directly from bee pollination (directly dependent crops, hereafter DD crops: e.g. apples, almonds, cherries, oranges, squash, vegetable and legume seeds, etc.), the total value of crops that do not require pollination but that are grown from seeds that result from pollination (indirectly dependent crops, hereafter ID crops: including field crops (legume hay, sugar beets, etc.) and vegetables (asparagus, broccoli, carrots, onions, etc.)) and 10% of the value of beef and dairy production resulting from the consumption of legume hay by cattle. Robinson, Nowogrodzki and Morse [59,60] and Morse and Calderone [61] present combined values for DD and ID crops but reduce the total gross values to reflect the estimated proportion due to honey bees; they do not include commodities further along the food chain. Southwick and Southwick [58] base their estimate of value on an analysis of supply and demand functions, defining value as "the surplus realized by consumers of these crops that would be lost if honey bees were depleted." Burgett, Rucker and Thurman [62] count only the value of pollination fees paid to beekeepers.

Several studies document the increasing cultivation and production of animal-pollinated crops on a global level [29–31,64]; however, studies specific to the US are lacking. Previous studies of insect pollination and US agriculture focus primarily on honey bees, a single year, or both. While those studies provide snapshots of the relationships between insect pollinators and US agriculture, they do not reveal trends in those relationships. Here, I present a comprehensive analysis of trends in aggregate production, cultivated area and farmgate value for 58 pollinator-

Table 5. Results of the analyses of aggregate data summed over all crops for each year.

Variable	y-intercept	B_1x	B_2x^2
Number of hectares of DD crops[1]			
Estimate ± SE	26.1611±1.5039	1.2009±0.3781	−0.0499±0.0185
t	17.40	3.18	−2.69
$P>\|t\|$	<0.0001	<0.0015	<0.0071
Total R^2	0.7694	na	na
Hectares of DD crops as a % total farm hectares			
Estimate ± SE	6.6394±0.1189	0.2841±0.0347	−0.008438±0.001910
t	55.85	8.19	−4.42
$P>\|t\|$	<0.0001	<0.0001	<0.0001
Total R^2	0.9190	na	na
Number of hectares of ID crops[1]			
Estimate ± SE	15.6404±0.1231	0.1617±0.0475	−0.0194±0.003536
t	127.04	3.40	−5.47
$P>\|t\|$	<0.0001	<0.0007	<0.0001
Total R^2	0.9185	na	na
Hectares of ID crops as a % total farm hectares			
Estimate ± SE	3.9633±0.0325	0.0602±0.0123	−0.005318±0.000909
t	121.96	4.90	−5.85
$P>\|t\|$	<0.0001	<0.0001	<0.0001
Total R^2	0.8898	na	na
Production DD crops[1]			
Estimate ± SE	97.0807±4.1440	3.8967±1.2232	−0.1403±0.0683
t	23.43	3.19	−2.05
$P>\|t\|$	<0.0001	<0.0014	<0.0400
Total R^2	0.6477	na	na
Production ID crops[1]			
Estimate ± SE	108.2111±2.8688	1.1554±0.6792	−0.1019±0.0372
t	37.72	1.70	−2.74
$P>\|t\|$	<0.0001	<0.0889	<0.0061
Total R^2	0.5777	na	na

[1]millions; DD = directly dependent crops; ID = indirectly dependent crops; x = year; na = not applicable; df = 1 all effects.
doi:10.1371/journal.pone.0037235.t005

dependent crops over an 18 year period from 1992–2009. I distinguish between, and report separately, statistics for DD and ID crops; and I present values for both honey bees and non-*Apis* pollinators. The primary goal in modeling these trends is to quantify the degree of dependence of US agriculture on insect pollinators and to determine if that dependence is declining, stable or increasing. To illuminate the contributions of individual crops, I present three, single-year snapshots (2002, 2007 and 2010). Additionally, I discuss dependency coefficients and valuation methods, two issues relevant to efforts to quantify the contributions of insect pollinators to agriculture. Lastly, I examine the question of a pollinator shortage in the US.

Materials and Methods

US population and farm data

General methods and sources of US population and farm data. Data on land in farms and the value of cropland were obtained from USDA National Agricultural Statistics Service (NASS: Farms and Land in Farms - Final Estimates 1993–97, 1998–2002, 2003–2007; Farms and Land in Farms 02-26-1999, 02-12-2010; Agricultural Land Values and Cash Rents – Final Estimates 1993–2003, 2004–2008; Land Values and Cash Rents 2010 Summary; and the 1997, 2002 and 2007 NASS Census of Agriculture reports) [65–87]. Acres were converted to hectares. Nominal values in USD were converted to 2009 USD (Table 1) using the CPI Index from the US Department of Labor, Bureau of Labor Statistics [88].

Trend analysis for US population and general farm data. I examined trends for the following variables for general farm and population data: 1) US population; 2) total hectares in farms; and 3) value of US cropland (2009 USD).

Crop data

General methods and sources of crop data. I obtained data for 58 pollinator-dependent crops from 1992 to 2009. Data for production, units of production, cultivated acres (planted acres when available, otherwise harvested/bearing acres) and the value of production were obtained from NASS (Final Estimates for 1986–2007, Annual Reports for 2008 and 2009, and the 2002 and 2007 Census of Agriculture (COA) reports) [89–108]. Production data for each crop in crop-specific units (e.g. cwt, boxes, etc.) were converted to common units (tonnes); cultivated acres were converted to hectares. Aggregate yield for each year was estimated by dividing total aggregate production in tonnes summed over all crops by the corresponding total aggregate number of cultivated hectares. Nominal values in USD were converted to 2009 USD.

For each year, the number of hectares of DD crops expressed as a percentage of total hectares in farms (Table 2) was calculated by dividing the annual aggregate number of hectares of DD crops by the corresponding total number of hectares in farms. For each year, the total number of hectares of DD crops expressed as hectares per person was calculated by dividing the aggregate number of hectares of DD crops by the corresponding estimate for the US population (Table 2). Corresponding estimates for production were calculated using the same method (Table 3). Equivalent estimates were calculated for ID crops (Table 2 and Table 3).

Partitioning value data. Partitioning value among honey bees and non-*Apis* pollinators was based on published coefficients of dependency [59,60]. The proportion attributed to non-*Apis* pollinators was calculated as the difference between the portion of total crop value attributed to all insect pollinators and the portion attributed to honey bees [63]. In the case of ID crops, the assignment was based on the dependency coefficients for the production of the seeds used to produce those crops [59,60]. For alfalfa hay, I generated a preliminary revision of the estimated proportions of value due to honey bees, leafcutter bees and other insect pollinators based on a review of production data for alfalfa seed (see Text S1).

Trend analysis for annual US crop and colony data

I examined trends for the following variables aggregated over all crops on an annual basis: 1–2) total number of cultivated hectares for both DD crops and ID crops; 3–4) total number of cultivated hectares for both crop groups as a percentage of total hectares in farms; 5–6) total production in tonnes for both groups; 7–8) aggregate yield for both groups; 9–10) number of cultivated hectares per person for both groups; 11–12) total production in tonnes per person for both groups; 13–14) total value (2009 USD) of production for both groups; 15–21) portions of total value for

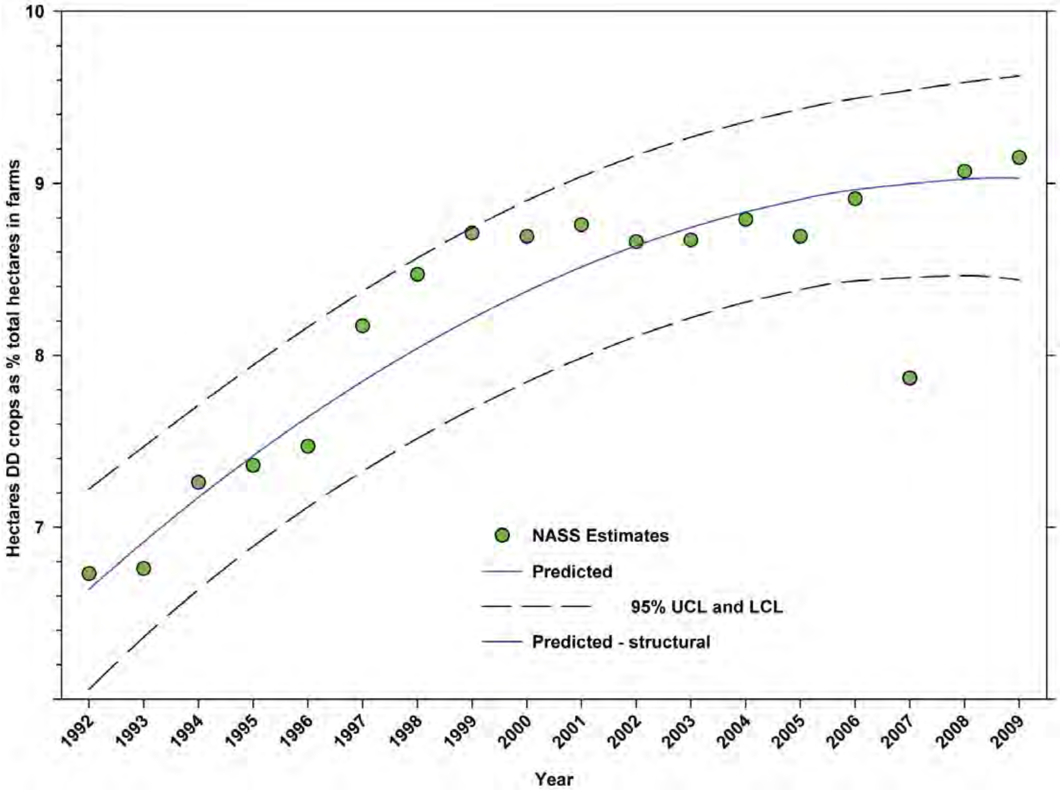

Figure 6. Hectares of directly dependent crops as a percentage of total hectares in farms. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g006

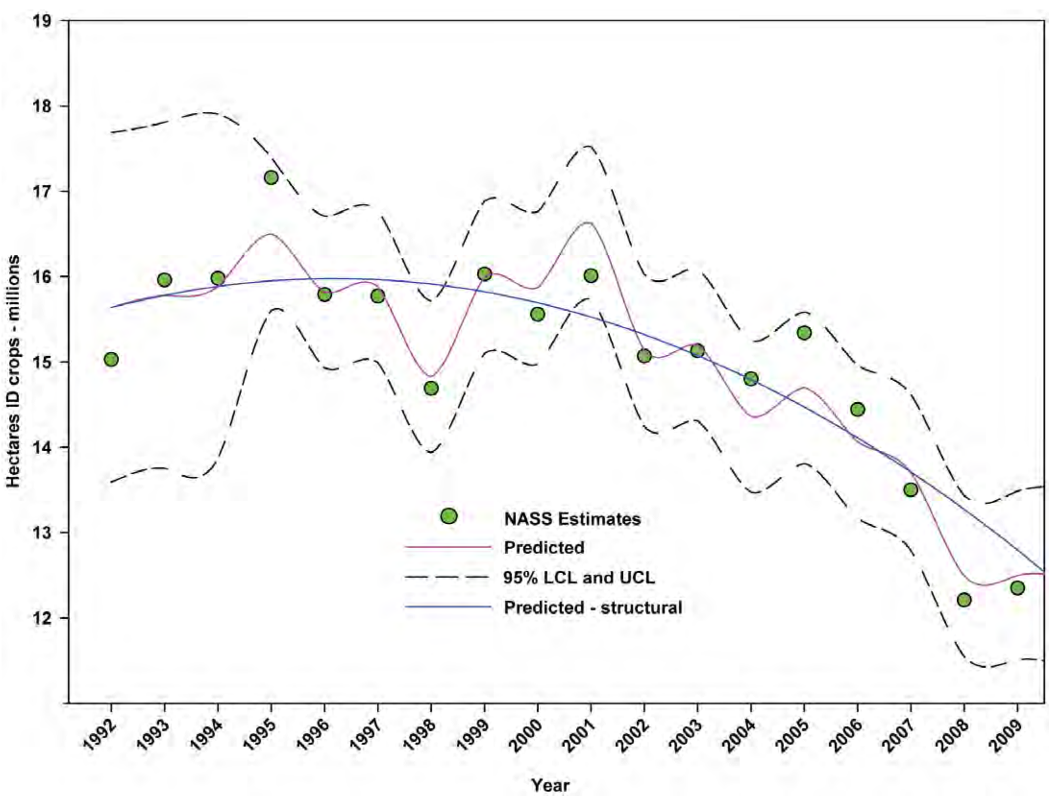

Figure 7. Number of hectares of indirectly dependent crops in the United States. Predicted values (pink) include adjustments for serial autocorrelation. Predicted – structural values (blue) are based solely on the structural elements of the model. ID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g007

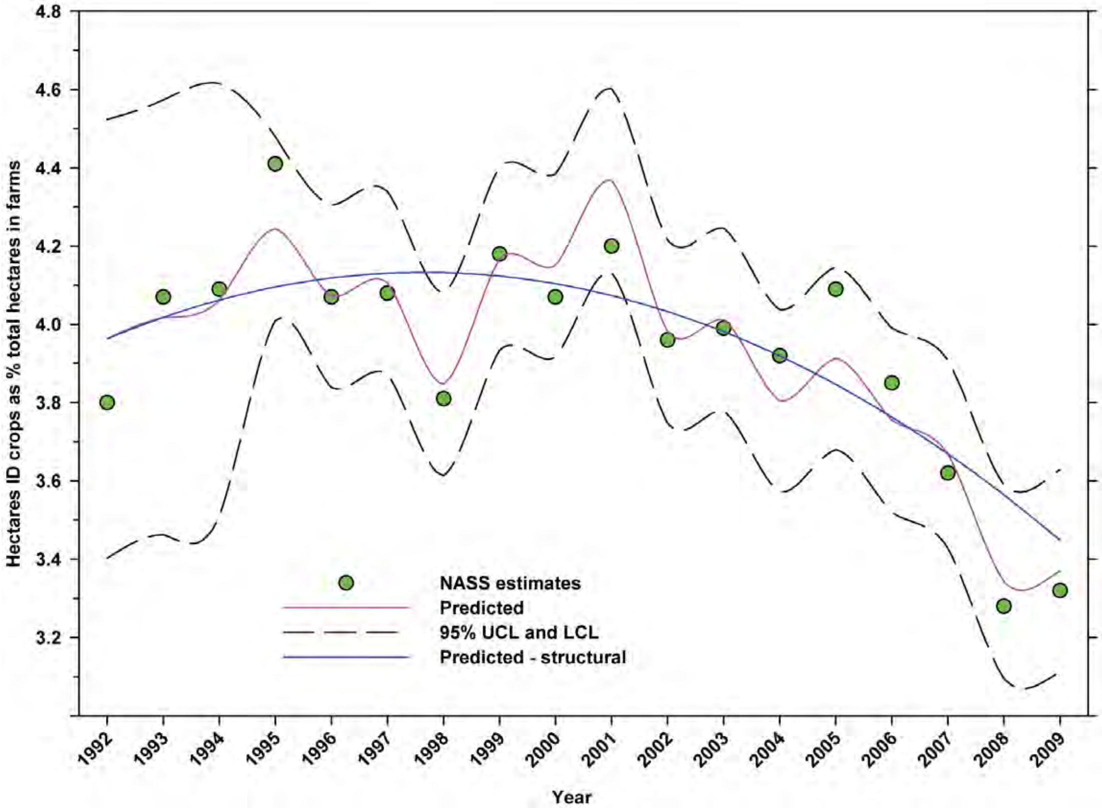

Figure 8. Hectares of indirectly dependent crops as a percentage of total hectares in farms. Predicted values (pink) include adjustments for serial autocorrelation. Predicted – structural values (also blue) are based solely on the structural elements of the model. ID = indirectly dependent.
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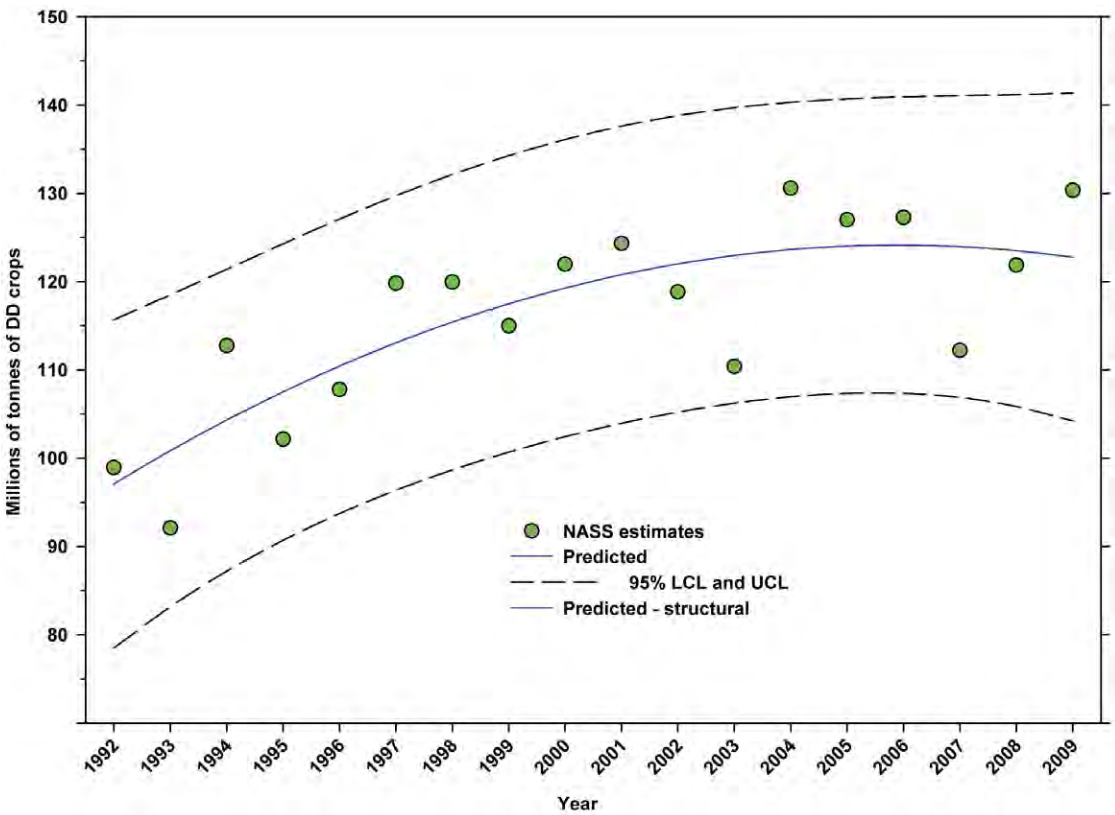

Figure 9. Total production (tonnes) of directly dependent crops. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g009

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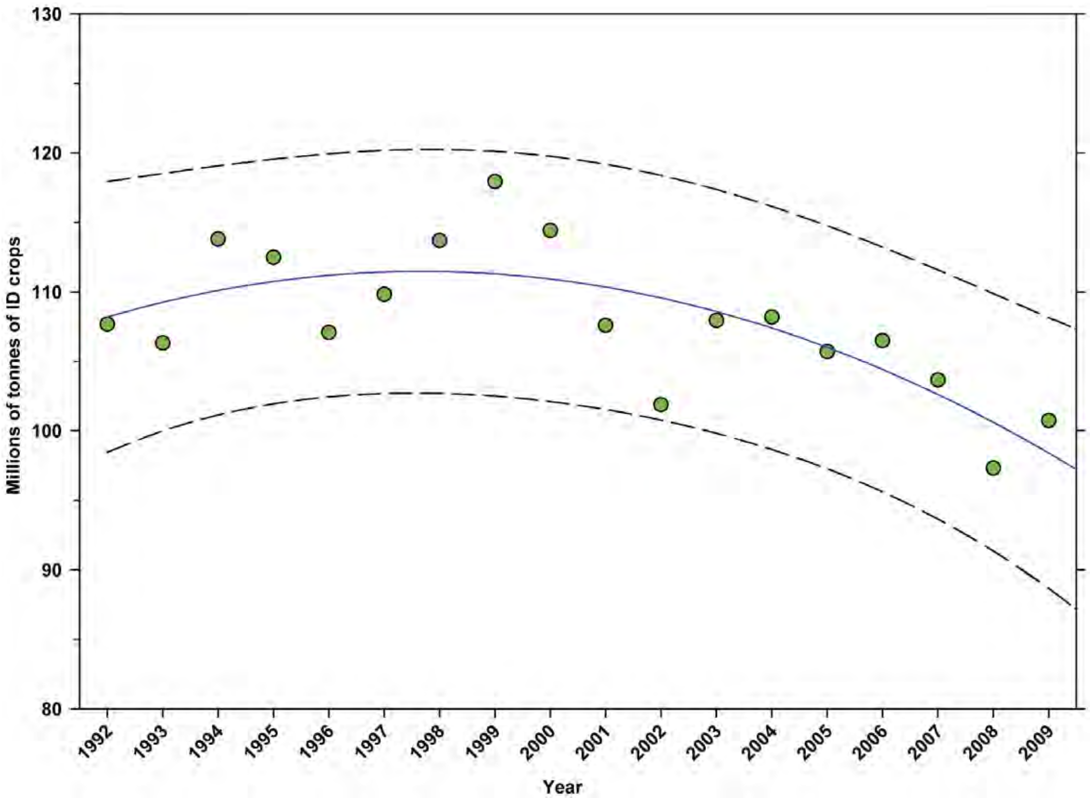

Figure 10. Total production (tonnes) of indirectly dependent crops. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g010

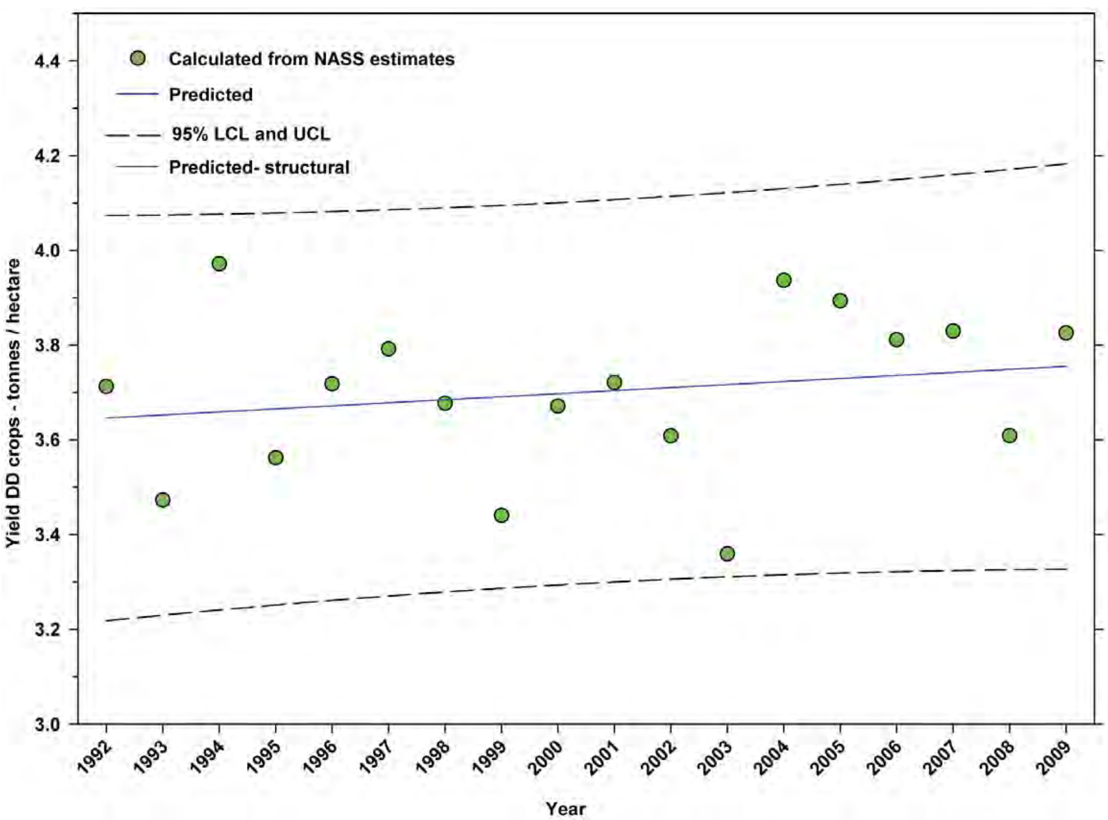

Figure 11. Yield of directly dependent crops. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g011

PER 000345

Table 6. Results of the analyses of aggregate data summed over all crops for each year.

Variable	y-intercept	B_1x	B_2x^2
Yield[1] of DD crops			
Estimate ± SE	3.6460±0.0832	0.006412±0.009121	na
t	43.82	0.70	na
P>|*t*|	<0.0001	<0.4821	na
Total R^2	0.0429	na	na
Yield[1] of ID crops			
Estimate ± SE	6.7602±0.1760	0.0524±0.0168	na
t	38.42	3.11	na
P>|*t*|	<0.0001	0.0019	na
Total R^2	0.3701	na	na

[1]Yield calculated as tonnes/hectare from production data and cultivated hectares; DD = directly dependent crops; ID = indirectly dependent crops; *df* = 1 all effects; na = not applicable.
doi:10.1371/journal.pone.0037235.t006

both groups attributed to insect pollination, honey bees, alfalfa leafcutter bees and other insects.

General analysis

Trends. Data were analyzed using regression analysis (PROC AUTOREG [109] with corrections for serial autocorrelation and/or heteroscedacity of variances where required to satisfy the assumptions of the analysis) with year as the independent variable. Trend analysis was limited to the period from 1992 through 2009 when there were no changes in the actual crops considered. Analysis of crop values was further limited to the period from 1996 to 2009 due to the inability to model data over the entire period from 1992 to 2009 (data for 1992–1995 are provided for informational purposes). Separate analyses were performed for DD and ID crops.

Data for individual crops. I report data for individual crops for the years 2002 and 2007 to illuminate the contributions of individual crops. Those years were selected because they are the most recent for which NASS Final Estimates and COA data were available [86,87]. Using COA data allowed for the inclusion of data for crops not available on an annual basis (alfalfa and non-alfalfa legume seed production, pumpkins and squash) and makes totals for most variables slightly higher than corresponding values presented in the trend analyses for those years. Data for individual crops for 2010 [107,108,110–112] are also presented.

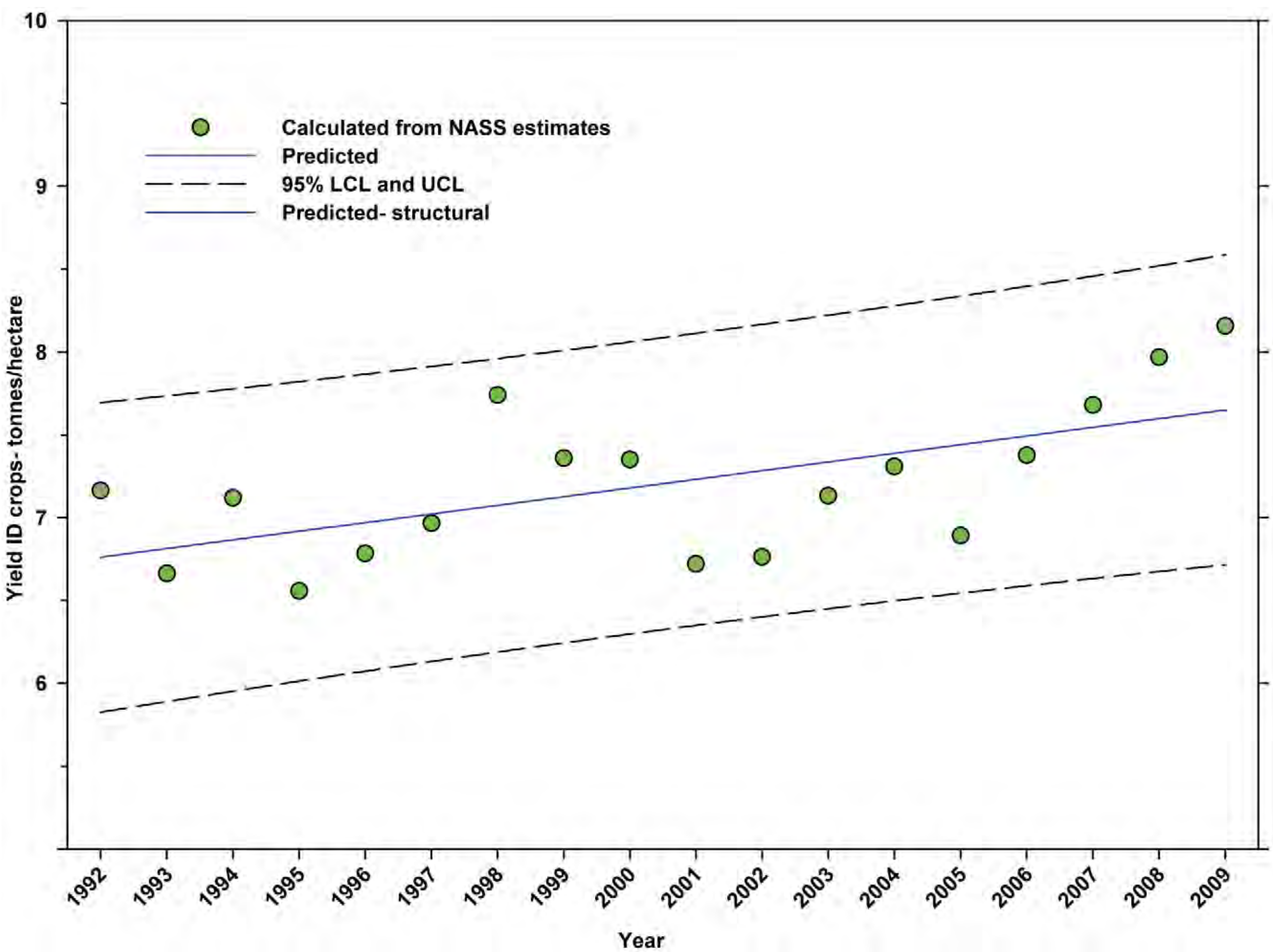

Figure 12. Yield of indirectly dependent crops. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g012

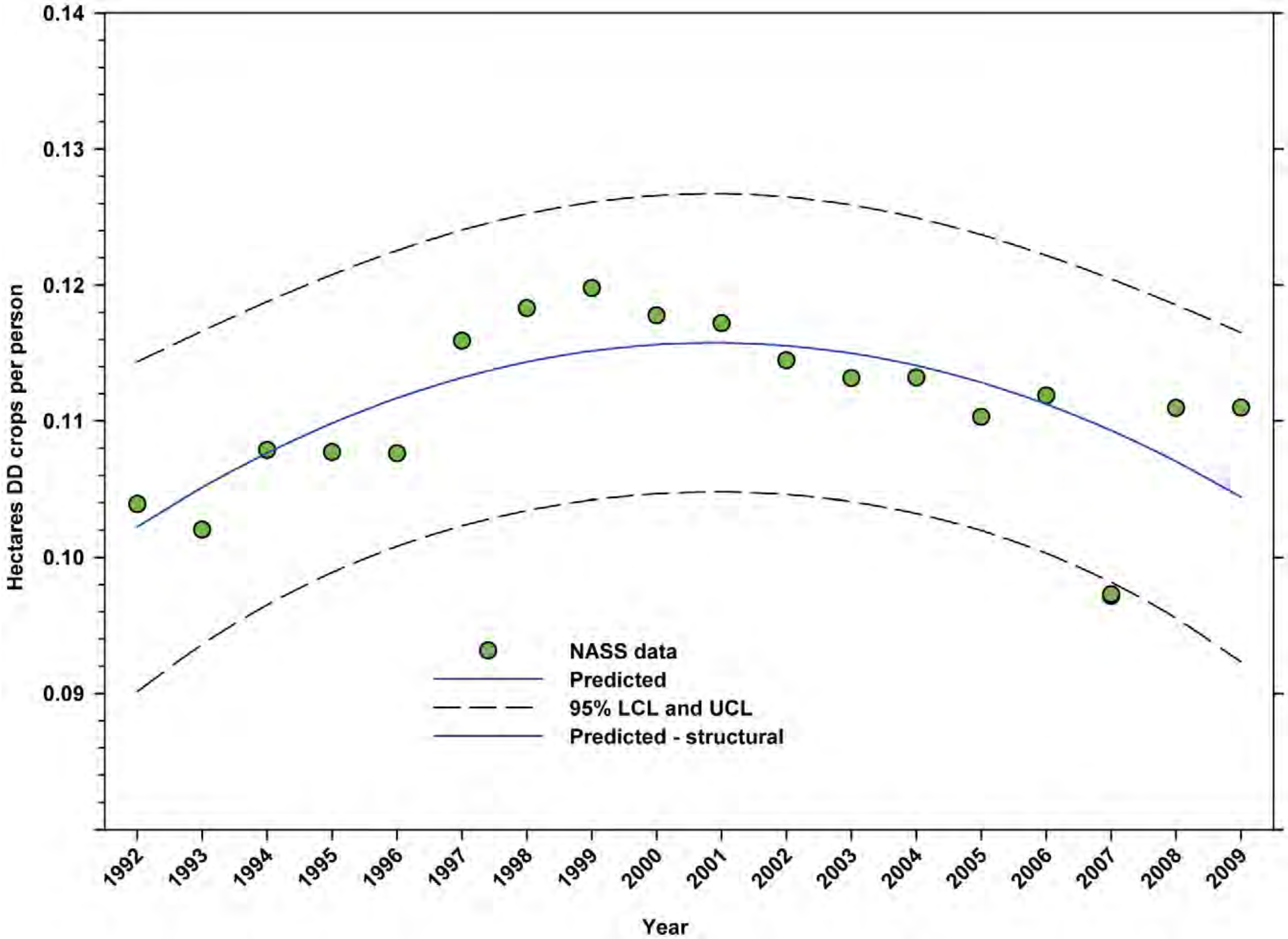

Figure 13. Hectares of directly dependent crops per person in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g013

Decline in the number of honey bee colonies and the pollinator shortage

The decline in the number of honey bee colonies [113–119], the number of colonies required to meet current recommendations (colonies per hectare) and their relationship to the adequacy of pollination services are analyzed.

Other issues and underestimates

Vegetable seeds. Data for vegetable seeds are no longer collected by NASS and are not included in any current estimates. Previous estimates [59,60] attribute 100% of vegetable seed production to insect pollination, with 90% of that due to honey bee pollination and 10% to other insects.Morse and Calderone [61] estimated that vegetable seed was worth an average of $61 million between 1996 and 1998.This could translate into an underestimate of $81.19 million (2009 USD) for DD crops for 2009, assuming no change in production.

Cotton lint. Cotton lint is produced from seed that requires insect pollination, making it a crop that benefits indirectly from pollination. However, lint production also benefits directly from having honey bees and other pollinators present during bloom [120,121]. Therefore, value data are included for both direct and indirect contributions; however, to avoid duplication of data for production and cultivated hectares, those metrics are reported only as an indirect crop.

Tomatoes. Tomatoes are not included in the present study; however, fresh and processed tomatoes were valued at approximately $2.5 billion in 2009 [122] (2009 USD) with some undetermined proportion due to non-*Apis* insect pollinators [123].

Bumblebees. Bumblebees are a major pollinator of many greenhouse crops, including tomatoes [124,125], peppers [126] and some berries [127–129]. They are also highly efficient pollinators of many field crops, including blueberries and cranberries (*Vaccinium* spp.) [130,131]. Bumblebees are available commercially, typically as nests of 150 or 300 workers or as 'quads' with 600–1,200 bees; however, national data on the economic contributions of wild and managed bumblebees are not available. This results in an underestimate of the value of insect pollination and the value of non-*Apis* pollinators in particular.

Results

Results of Trend Analysis for US population and general farm data

Between 1992 and 2009, the US population increased in a linear manner from 256.51 million to 307.01 million, an increase of 19.69% (Fig. 2; Table 4). Between 1992 and 2009, the total

Table 7. Results of analyses of aggregate date summed over all crops for each year.

Variable	y-intercept	B_1x	B_1x
Hectares of DD crops per person			
Estimate ± SE	0.1022±0.004824	0.003047±0.001218	−0.000172±0.0000601
t	21.20	2.50	−2.86
P>|*t*|	<0.0001	<0.0001	0.0042
Total R^2	0.5084	na	na
Hectares of ID crops per person			
Estimate ± SE	0.0611±0.000421	−0.000266±0.000178	−0.000052±0.0000136
t	145.06	−1.50	−3.79
P>|*t*|	<0.0001	<0.1356	<0.0001
Total R^2	0.9639	na	na
Tonnes of DD crops per person			
Estimate ± SE	0.4179±0.0152	0.0.0104±0.004644	−0.000535±0.000265
t	27.55	2.24	−2.02
P>|*t*|	<0.0001	<0.0253	<0.0432
Total R^2	0.2573	na	na
Tonnes of ID crops per person			
Estimate ± SE	0.4653±0.0106	−0.001517±0.002586	−0.000299±0.000146
t	43.99	−0.59	−2.05
P>|*t*|	<0.0001	<0.5576	<0.0407
Total R^2	0.8793	na	na

DD = directly dependent crops; ID = indirectly dependent crops; x = year; na = not applicable; *df* = 1 all effects.
doi:10.1371/journal.pone.0037235.t007

number of hectares in farms declined from 395.99 million to 372.23 million, a decline of 6.00% (Fig. 3; Table 4). The value (2009 USD) of cropland rose from $4,194.81 per hectare in 1997 to $6,597.71 in 2009 (Fig. 4; Table 4), an increase of 57.28%.

Results of Trend Analysis for Crops

Total number of cultivated hectares. The number of hectares of DD crops increased from 26.65 million in 1992 to 34.07 million in 2009, an increase of 27.84% (Fig. 5; Table 5) with most of that increase coming between 1992 and 2004 followed by a slight decline. The reduction in 2007 (data not included in analysis) was due to a transient reduction in hectares in soybeans and, to a lesser extent, peanuts. The percentage of total hectares in farms used for the production of DD crops increased from 6.73% in 1992 to 9.15% in 2009, an increase of 35.96% (Fig. 6; Table 5). The rate of increase slowed around 1999 but maintains an upward trend.

Over the same period, the number of hectares of ID crops declined from 15.03 million to 12.35 million, a decline of 17.83%. There was a slight increase between 1992 and 1996 followed by an accelerating decline thereafter (Fig. 7; Table 5). The number of hectares used for ID crops as a percentage of total hectares in farms declined from 3.80% in 1992 to 3.32% in 2009, a decline of 12.63% (Fig. 8; Table 5).

Total production. There was an increase in the production of DD crops from 98.93 million tonnes in 1992 to 130.34 million tonnes in 2009, an increase of 31.75% (Fig. 9; Table 5), although the rate of increase slowed around 1999. Production of ID crops decreased over the same period from 107.67 million tonnes in 1992 to 100.74 million tonnes in 2009, a decline of 6.44% (Fig. 10; Table 5). Production increased between 1992 and 1999 but declined thereafter.

Yield. For the period from 1992–2009, the yield of DD crops ranged between 3.97 tonnes per hectare (1994) and 3.36 tonnes per hectare (2003); but there was no significant trend (Fig. 11; Table 6). For the same period, the yield of ID crops exhibited a significant increasing linear trend from 7.16 tonnes per hectare in 1992 to 8.16 tonnes/hectare in 2009 (Fig. 12; Table 6).

Response to changes in US population. The number of hectares of DD crops expressed as hectares per person (Table 2) rose from 1992 to 1999 when it peaked at 0.1198, but declined to 0.1110 by 2009 (Fig. 13; Table 7). The production of DD crops expressed as tonnes per person (Table 3) rose from 1992 to 2001 when it reached 0.48, but has since trended downward (Fig. 14; Table 7). The number of hectares of ID crops expressed as hectares per person (Table 2) declined steadily from 1992 through 2009 from 0.06 to 0.04 (Fig. 15; Table 7). Production of ID crops expressed as tonnes per person followed a similar pattern, reaching a high of 0.48 in 1994 and declining to 0.36 by 2009 (Fig. 16; Table 7).

Total value (2009 USD). The total value of DD crops decreased from $52.18 B in 1996 to $36.30 B in 2001, but increased thereafter, reaching $55.99 B in 2009, an increase of 7.30% since 1996 and 54.24% from the low in 2001 (Fig. 17; Table 8). The total value of ID crops declined from $23.95 B in 1996 through 2001, but has since increased, reaching $16.03 B in 2009. Overall, this reflects a decline of 33.07% (Fig. 18; Table 8); however, the value of $16.03 B in 2009 was well below the trend line, and the value in 2008 was $18.31 B.

Total value attributed to insect pollination (2009 USD). The value of DD crops attributed to insect pollination decreased from $14.29 B in 1996 to $10.69 B in 2001, but increased thereafter, reaching $15.12 B in 2009, an increase of 41.44% since the low in 2001 (Fig. 19; Table 8). The value of ID crops attributed to insect pollination declined from $15.45 B in 1996 to $11.80 B in 2009, a decline of 23.63% (Fig. 20; Table 8); although the 2009 value was below the trend line. This metric has increased since 2004.

Total value attributed to honey bees (2009 USD). The value of DD crops attributed to honey bee pollination decreased from $11.20 B in 1996 to $8.33 B in 2001, but increased thereafter, reaching $11.68 B in 2009, an increase of 40.22% from the low in 2001 (Fig. 21; Table 9). The value of ID crops attributed to honey bees decreased from $7.33 B in 1996 to $5.39 B in 2009, a decrease of 26.47% (Fig. 22; Table 9). The decline occurred between 1996 and 2004 and values trended upward thereafter with the exception of 2009 which was below the trend line.

Total value attributed to M. rotundata (2009 USD). The leafcutter bee is responsible for the major portion of alfalfa seed (data not available on annual basis) and, indirectly, alfalfa hay. The value of alfalfa hay attributed to leafcutter bees ranged between $4.99 B (2003) and $7.04 B (2008) (Fig. 23; Table 9) with a decline to $5.26 B in 2009. With that exception, the overall trend has been increasing since 2003.

Total value attributed to other insects (2009 USD). The value of DD crops attributable to insect pollinators other than honey bees or leafcutter bees decreased from $3.09 B in 1996 to $2.36 B in 2001, but increased thereafter, reaching $3.44 B in 2009, increase of 45.76% from the low in 2001 (Fig. 24; Table 9). The value of ID crops attributable to insect pollination other than honey bees or leafcutter bees decreased over the same period from

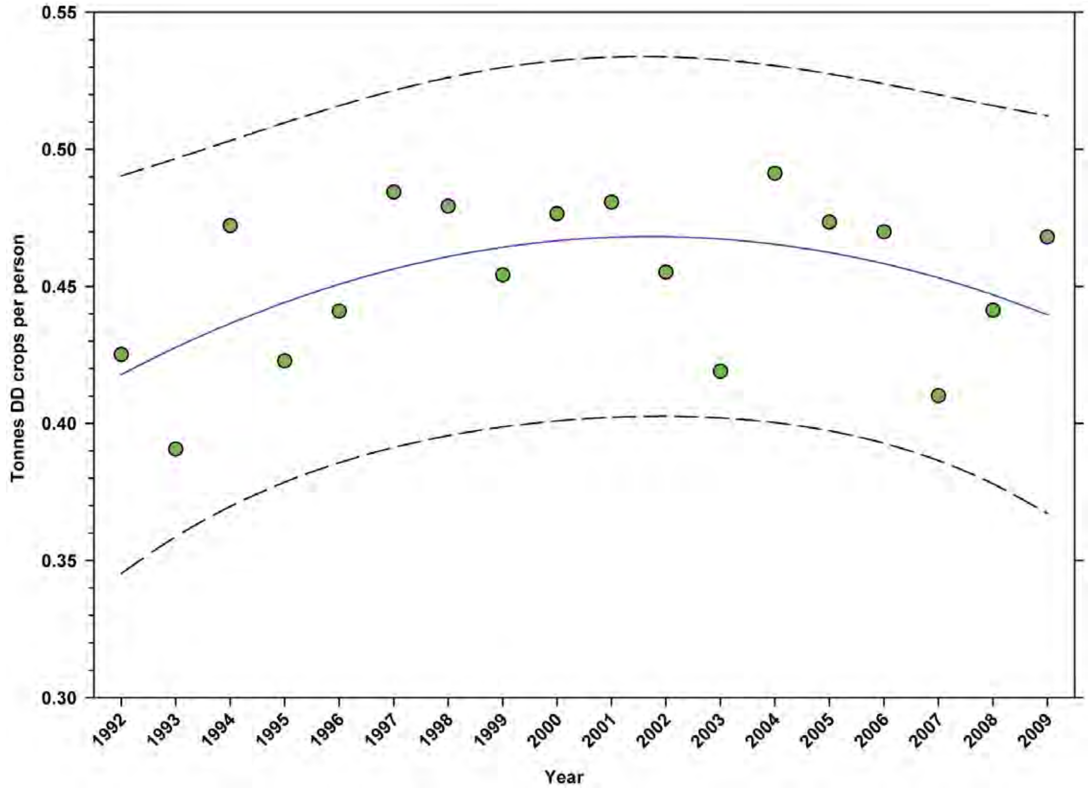

Figure 14. Tonnes of directly dependent crops per person in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g014

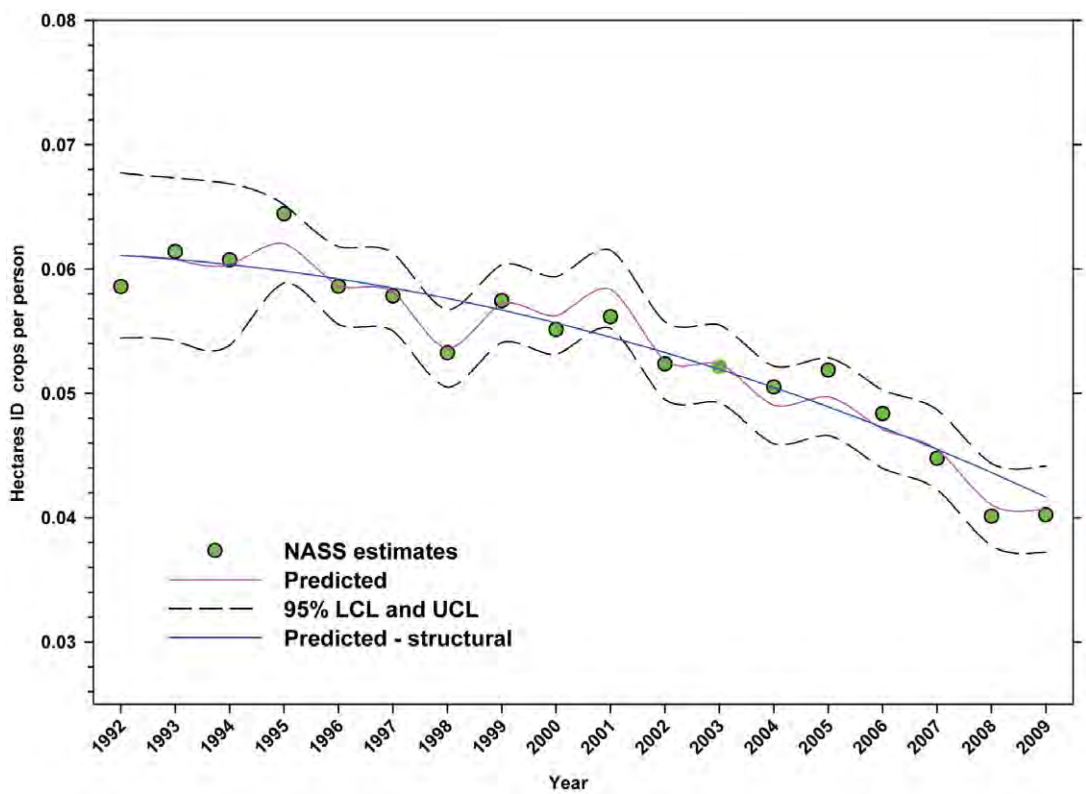

Figure 15. Hectares of indirectly dependent crops per person in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g015

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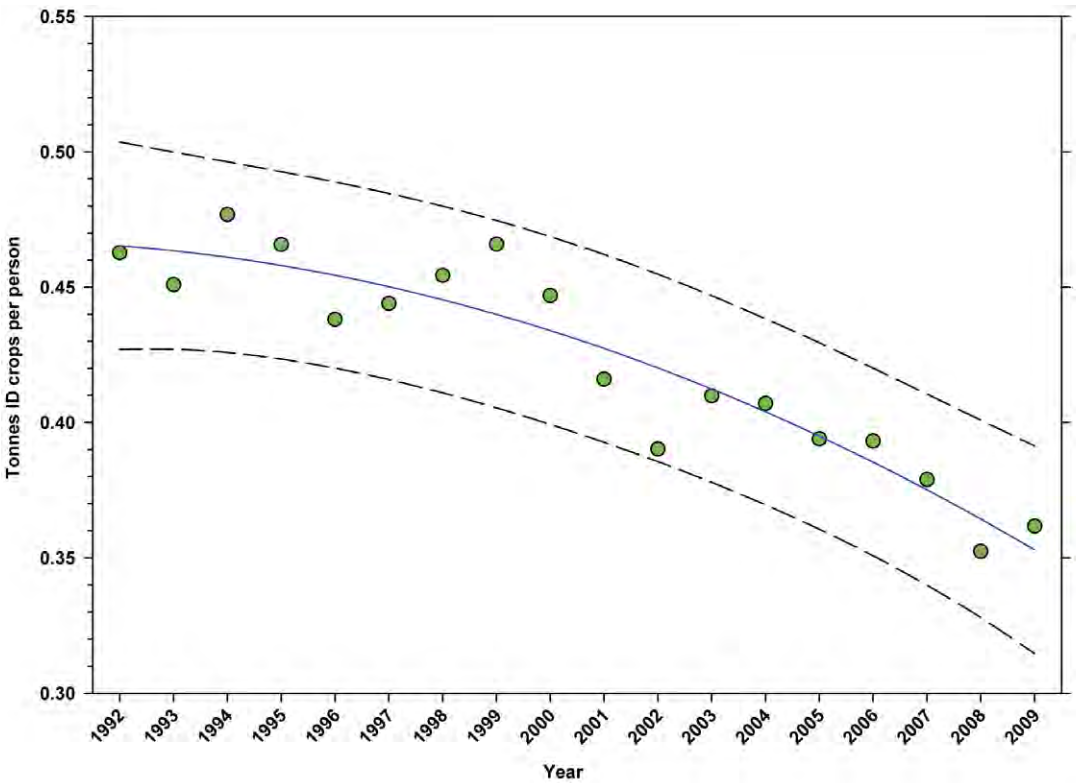

Figure 16. Tonnes of indirectly dependent crops per person in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g016

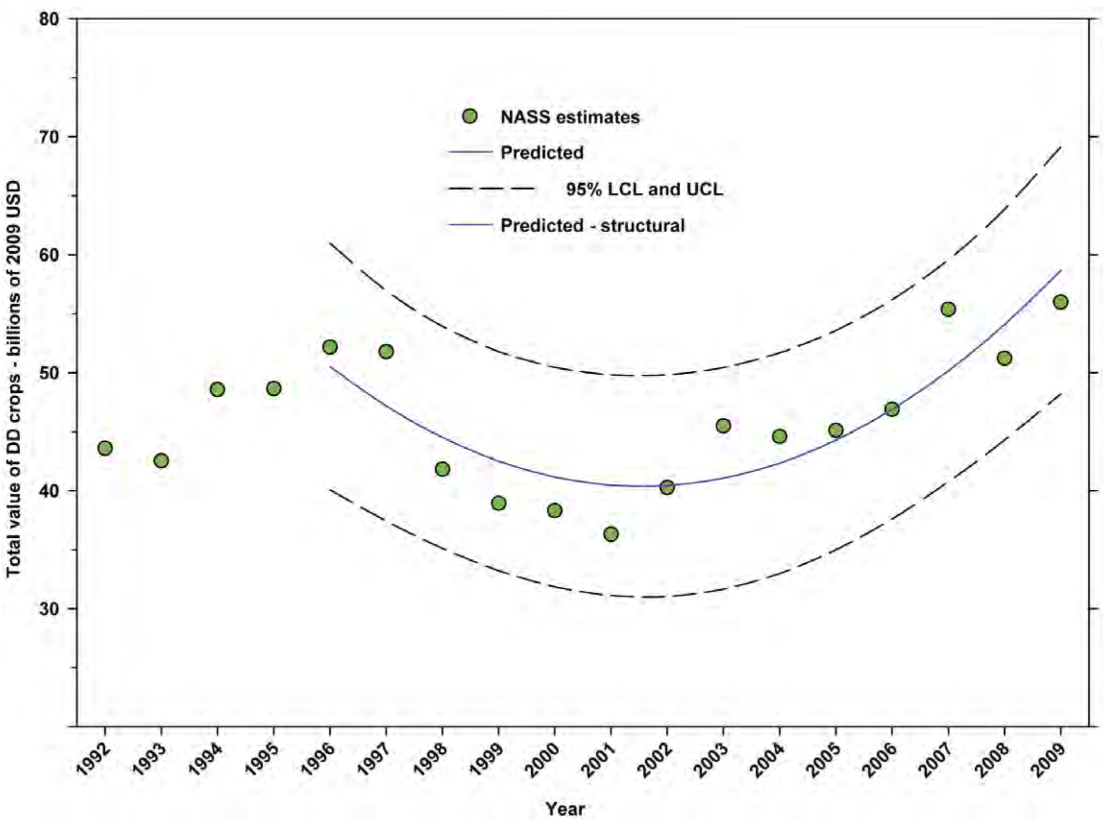

Figure 17. Total value of directly dependent crops. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g017

Table 8. Statistics for aggregate values from 1996–2009.

Variable	*y*-intercept	B_1x	B_2x^2
Total value DD crops - billions of 2009 USD			
Estimate ± SE	50.5281±2.3798	−3.6651±0.8850	0.3302±0.0655
t	21.23	−4.14	5.04
$P>\|t\|$	<0.0001	<0.0001	<0.0001
Total R^2	0.7475	na	na
Total value ID crops - billions of 2009 USD			
Estimate ± SE	22.8607±0.9418	−1.2576±0.3803	0.0708±0.0270
t	24.27	−3.31	2.62
$P>\|t\|$	<0.0001	<0.0021	<0.0088
Total R^2	0.5985	na	na
Value DD crops due to insect pollination - billions of 2009 USD			
Estimate ± SE	13.6784±0.7478	−0.6670±0.2633	0.0677±0.0184
t	18.29	−2.53	3.68
$P>\|t\|$	<0.0001	<0.0113	<0.0002
Total R^2	0.6539	na	na
Value ID crops due to insect pollination -billions of 2009 USD			
Estimate ± SE	16.0180±0.7502	−0.9604±0.1861	0.0614±0.0115
t	21.35	−5.16	5.34
$P>\|t\|$	<0.0001	<0.0001	<0.0001
Total R^2	0.5206	na	na

DD = directly dependent crops; ID = indirectly dependent crops; x = year; na = not applicable; *df* = 1 all effects.
doi:10.1371/journal.pone.0037235.t008

$1.55 B to $1.15 B, a decline of 25.81% (Fig. 25; Table 9). The decline occurred between 1996 and 2000; values have been relatively stable or increasing since.

Statistics for individual crops for 2002 and 2007

Data for individual crops for 2002 and 2007 are presented as Text S2. Values for production, cultivated hectares and value of production are slightly greater than those shown in the trend analyses because they include data on alfalfa and non-alfalfa legume seed, pumpkins and squash, none of which were available for the trend analyses. Data for 2010 (data for legume seed production not available) are presented as Text S3.

Decline in the number of honey bee colonies and the pollinator shortage

An analysis of the decline in the number of honey bee colonies, the number of colonies required to meet current recommendations (colonies/hectare) and their relationship to the adequacy of pollination services are presented as Text S4.

Other hive products. National data on the US honey bee queen and package industries, nucs (starter colonies), pollination rental fees and hive products other than honey are not available. I place a tentative estimate of $300–$500 million (2009 USD) on the value of those products and services but do not include that estimate in any calculation.

Discussion

Summary of data for DD Crops

The number of cultivated hectares of DD crops increased from 26.65 million in 1992 (first year for production, cultivated area and yield data in this study) to 34.07 million in 2009, an increase of 27.84% (Fig. 5). As a percentage of total farm hectares, this represents an absolute increase from 6.73% to 9.15% and a relative increase of 35.96% (Fig. 6); this growth occurred as the price of cropland was also rising (Fig. 4), reflecting the relatively high value of those crops [28]. Production increased from 98.93 million tonnes in 1992 to 130.34 million tonnes in 2009, an increase of 31.75% (Fig. 9). The majority of increases in each metric occurred between 1992 and 2000/2001 with flat or significantly reduced rates of increase thereafter. Aggregate yield was flat over the study period (Fig. 11). US trends differ somewhat from those in other developed countries that show steady increases in yield and cultivated acres and more modest but continuing increases in production over the same period. They differ significantly from trends in the developing world where those metrics continue to increase rapidly [29,31]. The cultivated area and production of DD crops in the US, measured as hectares or tonnes per person, kept pace with growth in the population through 2000–2001, but neither kept pace thereafter (Fig. 13 and Fig. 14) even though per capita consumption of fruits and vegetables remained relatively steady [2–5]. These results are consistent with land use patterns reflecting rising cropland values and growing access to imported food [132–135].

The total value (2009 USD) of DD crops declined between 1996 (first year for value data in this study) and 2001 from $52.18 B to $36.30 B, but rose thereafter, reaching $55.99 B in 2009 (Fig. 17), an increase of 54.24% from 2001. Revenues attributed to insect pollination decreased from $14.29 B in 1996 to $10.69 B in 2001, but increased thereafter, reaching $15.12 B in 2009 (Fig. 19), an increase of 41.44% from 2001. Revenues attributed to honey bees decreased from $11.20 B in 1996 to $8.33 B in 2001, but increased thereafter, reaching $11.68 B in 2009 (Fig. 21), an increase of 40.22% since 2001. Revenues attributed to insect pollinators other than honey bees decreased from $3.09 B in 1996 to $2.36 B in 2001, but increased thereafter, reaching $3.44 B in 2009 (Fig. 24), an increase of 45.76% from 2001.

Summary of data for ID Crops

The number of hectares used for production of ID crops was relatively steady between 1992 and the early 2000's, but declined from a high of 16.03 million hectares in 1999 to 12.35 million in 2009, a reduction of 22.96% (Fig. 7). As a percentage of total farm hectares, this represents an absolute decline from 3.80% to 3.32% and a relative decline of 12.63% (Fig. 8). This may be due, in part, to the rising value of cropland (Fig. 4) and the fact that the value of ID crops tends to be less than that of DD crops [28]. Total production followed a similar pattern, declining from a high of 117.94 tonnes in 1999 to 100.74 tonnes in 2009, a reduction of 14.58% (Fig. 10). The fact that the decline in production (14.58%) was less than the decline in hectares (22.96%) can be explained, in part, by the increase in yield over the same period (Fig. 12). US trends are similar to those in other developed countries that show steady increases in yields of ID crops with declines in both production and cultivated area over the same period. They differ significantly from trends in the developing world where yield and production continue to increase rapidly while cultivated area also continues to increase, albeit at a somewhat slower rate [29,31]. Trend analysis revealed that neither hectares nor production of ID crops, measured as hectares or tonnes per person, kept pace with the growth in the US population (Fig. 15 and Fig. 16). As with DD crops, these results are consistent with land use patterns reflecting increasing cropland values and the availability of imported food [132–135].

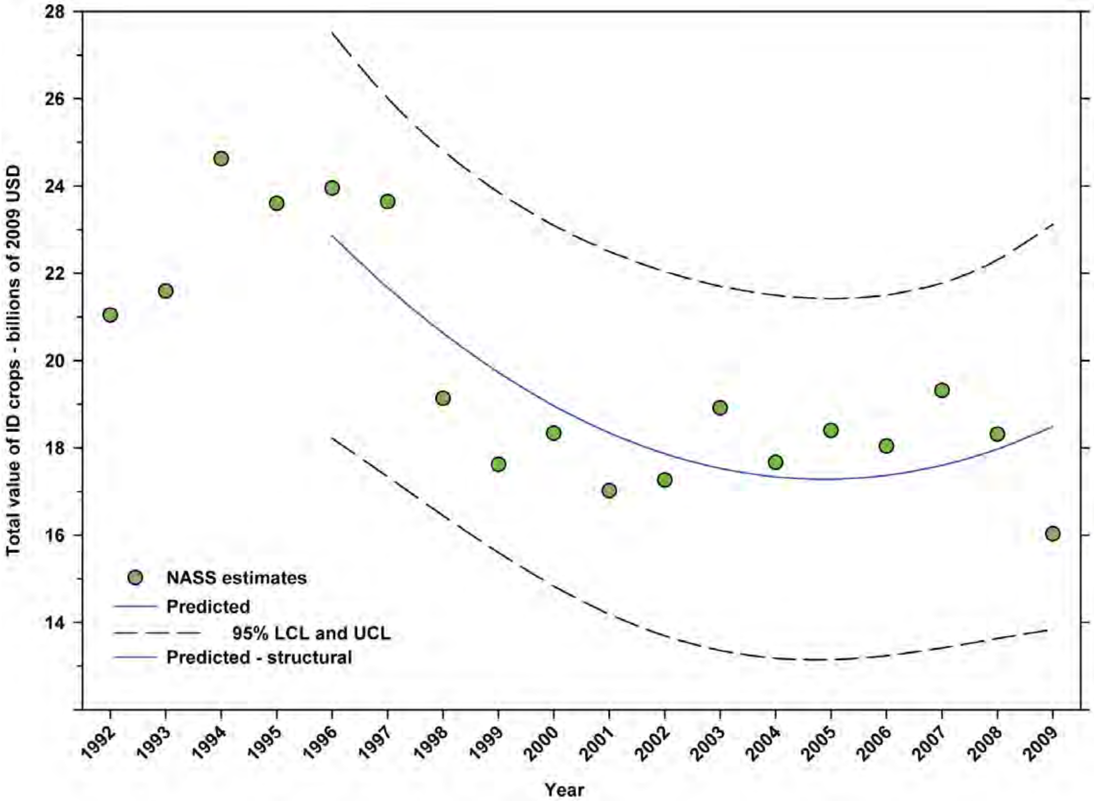

Figure 18. Total value of indirectly dependent crops. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g018

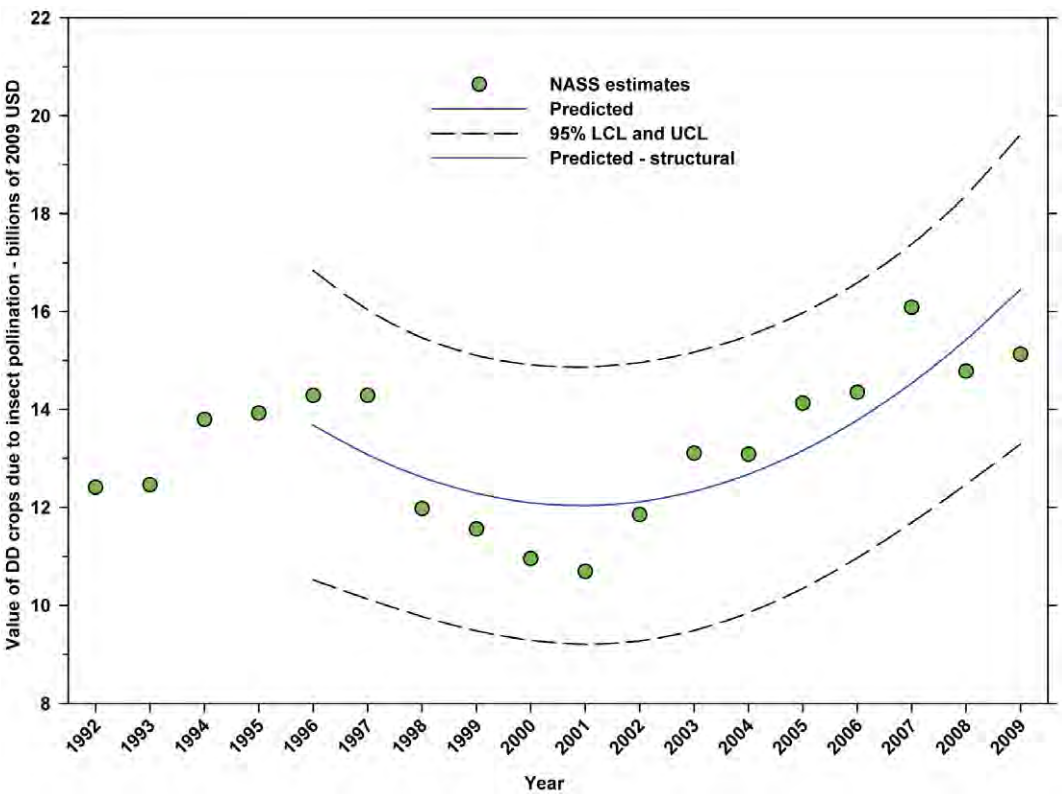

Figure 19. Value of directly dependent crops attributed to insect pollination. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g019

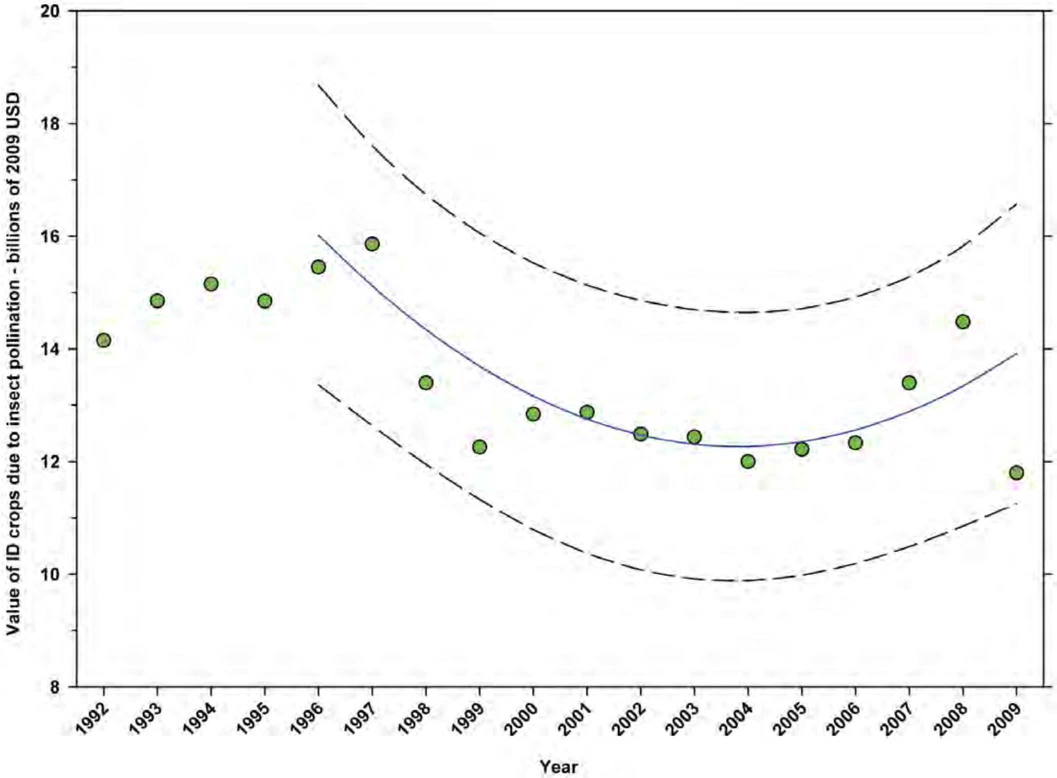

Figure 20. Value of indirectly dependent crops attributed to insect pollination. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g020

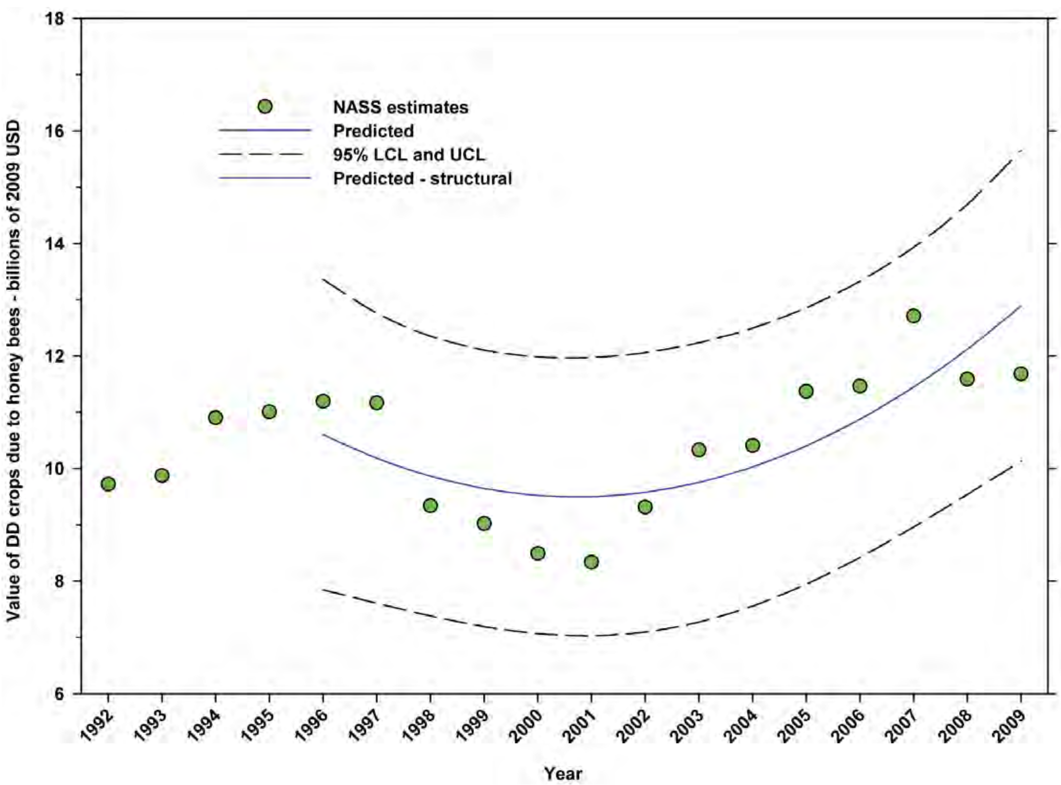

Figure 21. Value of directly dependent crops attributed to honey bees (*A. mellifera*). Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g021

Table 9. Statistics for aggregate values from 1996–2009.

Variable	*y*-intercept	B_1x	B_2x^2
Value DD crops due to *A. mellifera* - billions of 2009 USD			
Estimate ± SE	10.6028±0.6554	−0.4686±0.2261	0.0496±0.0157
t	16.18	−2.07	3.15
$P>\|t\|$	<0.0001	<0.0382	<0.0016
Total R^2	0.5972	na	na
Value ID crops due to *A. mellifera* -billions of 2009 USD			
Estimate ± SE	7.2810±0.2377	−0.3186±0.1074	0.0166±0.007319
t	30.63	−2.97	2.27
$P>\|t\|$	<0.0001	<0.0030	0.0232
Total R^2	0.6933	na	na
Value ID crops due to *M. rotundata* - billions of 2009 USD			
Estimate ± SE	6.8753±0.7324	−0.4772±0.2132	0.0324±0.0142
t	9.39	−2.24	2.29
$P>\|t\|$	<0.0001	<0.0252	<0.0221
Total R^2	0.4016	na	na
Value DD crops due to other non-*Apis* insect pollinators - billions of 2009 USD			
Estimate ± SE	3.0755±0.1126	−0.1988±0.0410	0.0182±0.003054
t	27.32	−4.84	5.95
$P>\|t\|$	<0.0001	≪0.0001	<0.0001
Total R^2	0.8269	na	na
Value ID crops due to other non-*Apis* insect pollinators - billions of 2009 USD			
Estimate ± SE	1.5184±0.0528	−0.0737±0.0233	0.004328±0.001627
t	28.75	−3.16	2.66
$P>\|t\|$	<0.0001	<0.0016	<0.0078
Total R^2	0.6265	na	na

DD = directly dependent crops; ID = indirectly dependent crops; x = year; na = not applicable; *df* = 1 all effects.
doi:10.1371/journal.pone.0037235.t009

The total value of ID crops declined from $23.95 B in 1996 to $17.01 B in 2001, but increased thereafter, ranging between $16.02 B (2009) and $19.32 B (2007) (Fig. 18). Revenues attributed to insect pollination declined from $15.45 B to $11.99 B between 1996 and 2004, but have since risen with the exception of 2009 which saw a large decline from $14.48 B in 2008 to $11.80 B in 2009 (Fig. 20). Revenues attributed to honey bees declined from $7.33 B in 1996 to $5.39 B in 2009 with values otherwise running between $6.40 B and $5.39 B since 1998 (Fig. 22). The value attributed to insect pollinators other than honey bees or leafcutter bees decreased over the same period from $1.55 B to $1.15 B (Fig. 25), although 2009 was well below the trend line. The value of alfalfa hay attributed to leafcutter bees ranged between $4.99 B (2003) and $ 7.04 B (2008) with decreasing values between 1996 and 2003 and increasing values thereafter (Fig. 23).

Dependency coefficients and value estimates

Two topics that influence efforts to quantify the contributions of insect pollinators to US agriculture are: 1) the accuracy of the dependency coefficients for partitioning value among the various pollinators [16,136], and 2) the interpretation of value [58,137]. With the exception of the coefficients for alfalfa seed and hay production, dependency coefficients used here come from Robinson, Nowogrodzki and Morse [59,60] who based estimates on a review of 275 studies conducted prior to 1989. To the degree that those estimates are sensitive to changes in management practices (e.g., selection of crop varieties; the use of pesticides, fertilizers and growth regulators; the size of fields or orchards) and local environmental factors (e.g., land-use patterns; the abundance and diversity of non-*Apis* pollinators), they may not reflect the current contributions of the various pollinator groups. In addition, the methodology of those studies was not usually designed to capture the contributions of non-*Apis* bees and other insects. Current research emphasizes the diversity and abundance of pollinator species combined with measures of blossom density, visits per blossom, pollen grains deposited per visit and yield [138–140]. Such studies promise to increase the accuracy of estimates of dependency coefficients in a variety of landscape situations.

The second topic involves the estimation of value. Most studies estimate the value of honey bee pollination as the increase in gross farmgate value over and above that expected in the absence of honey bees (see Mburu and colleagues [137] for discussion of valuation methods). However, this method has certain limitations. It focuses on gross rather than net income [141]; and it neglects to account for other inputs such as chemicals, fuel, equipment, labor, water and land [142]. Further, it differs from the way value is often used by economists because it does not account for the response of markets to changes in supply [28,58,142–144]. If honey bee populations were reduced or eliminated, it is argued, markets would adjust through some combination of factors, including the use of alternative pollinators, changes in the price of goods, and other changes in grower and consumer behavior, until a new

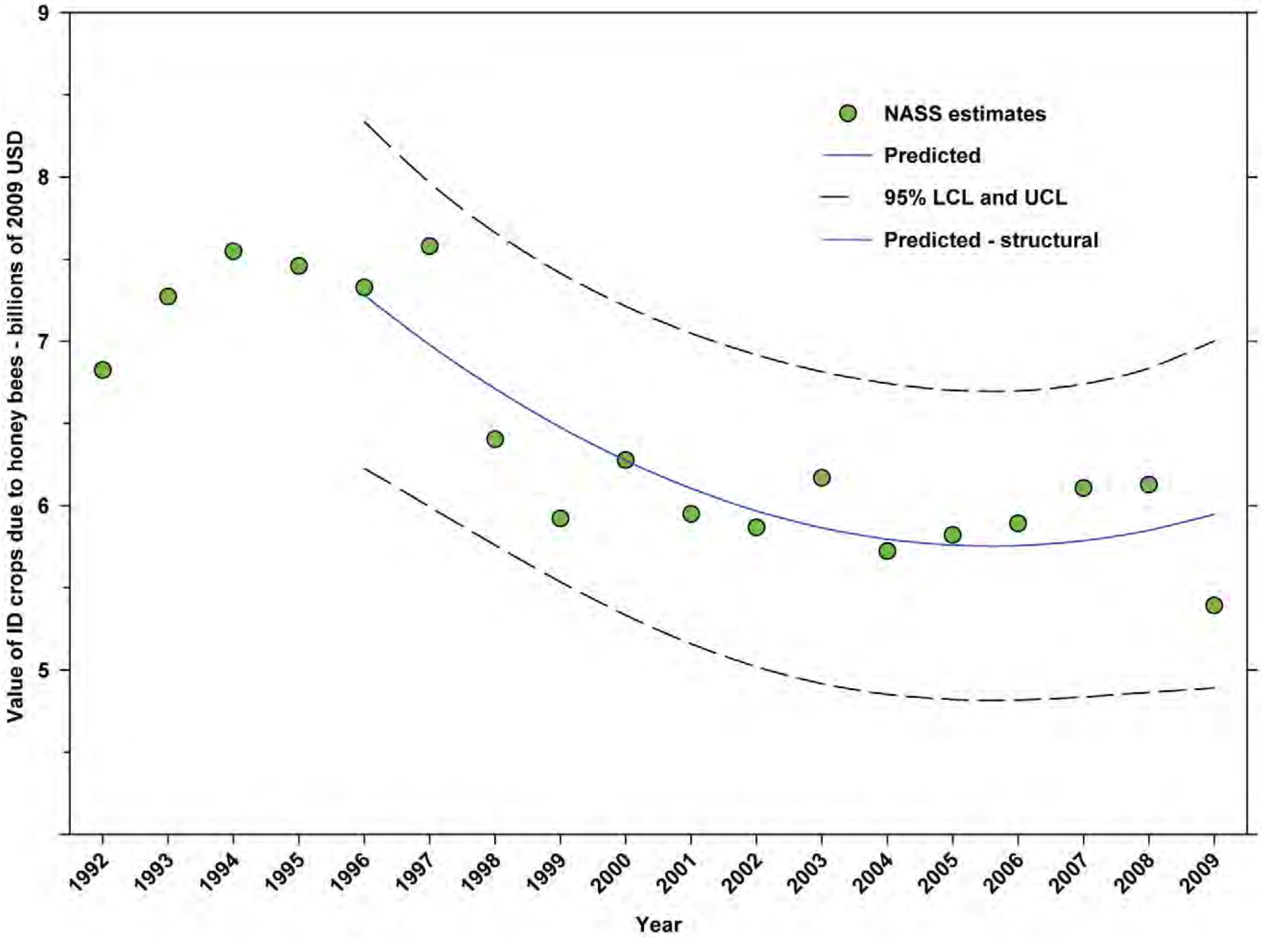

Figure 22. Value of indirectly dependent crops attributed to honey bees (*A. mellifera*). Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = directly dependent.
doi:10.1371/journal.pone.0037235.g022

equilibrium is established. The actual value of honey bees would be the difference between the original farmgate revenues and the new farmgate revenues received after market adjustments had produced a new steady state; therefore, a simple accounting approach provides only one perspective on value. It may be useful to think of value as used herein as an historical accounting of the additional gross revenues that have accrued to growers as a result of their having used honey bees, *caeteris paribus*.

A reduction in the availability of pollinators and pollinator dependent crops may have other consequences that are difficult to value. While a change in pollinator availability may lead to market adjustments involving changes in grower production and consumer consumption patterns, all such patterns are not equivalent. Assuming that current patterns without pollinator shortages reflect consumer preferences, changes in those patterns imposed by a loss of pollinators would necessarily reflect less desirable choices. Additionally, while the majority of calories are derived from crops that do not require animal pollination [29,145], the elimination of crops that do require animal pollination would result in a diet that is culturally impoverished and nutritionally inadequate due to a loss of micronutrients [51,146].

Non-*Apis* options for growers

One option available to growers in the event of a sustained loss of honey bees would be to use other pollinators. Non-*Apis* bees, both managed and wild, have great potential as commercial pollinators. Some are more efficient than honey bees on certain crops [145]; management systems for a few are well developed; and protocols for the development of systems for additional species have been proposed [147,148]. The horned-faced bee, *Osmia cornifrons*, was introduced to the US in 1977 from Japan [149] where it has been successfully used for apple pollination [150,151]. The blue orchard bee, *O. lignaria*, is useful on a variety of crops including almonds and cherries [147,152,153]. Management systems for both are well-developed; however, as with the honey bee, each has its own suite of pests, pathogens, predators and parasites. Scaling production to levels sufficient to replace honey bees on selected crops will take time, and difficulties may arise along the way.

Bumble bees are excellent generalist pollinators and are available commercially. Bumble bees forage at lower temperatures [154] and provide superior pollination on a bee-for-bee basis for some crops, including blueberries and cranberries [130]; however, they are expensive compared to honey bees (approximately 1.00–2.00 USD per bumble bee versus 0.01–0.02 USD per honey bee).

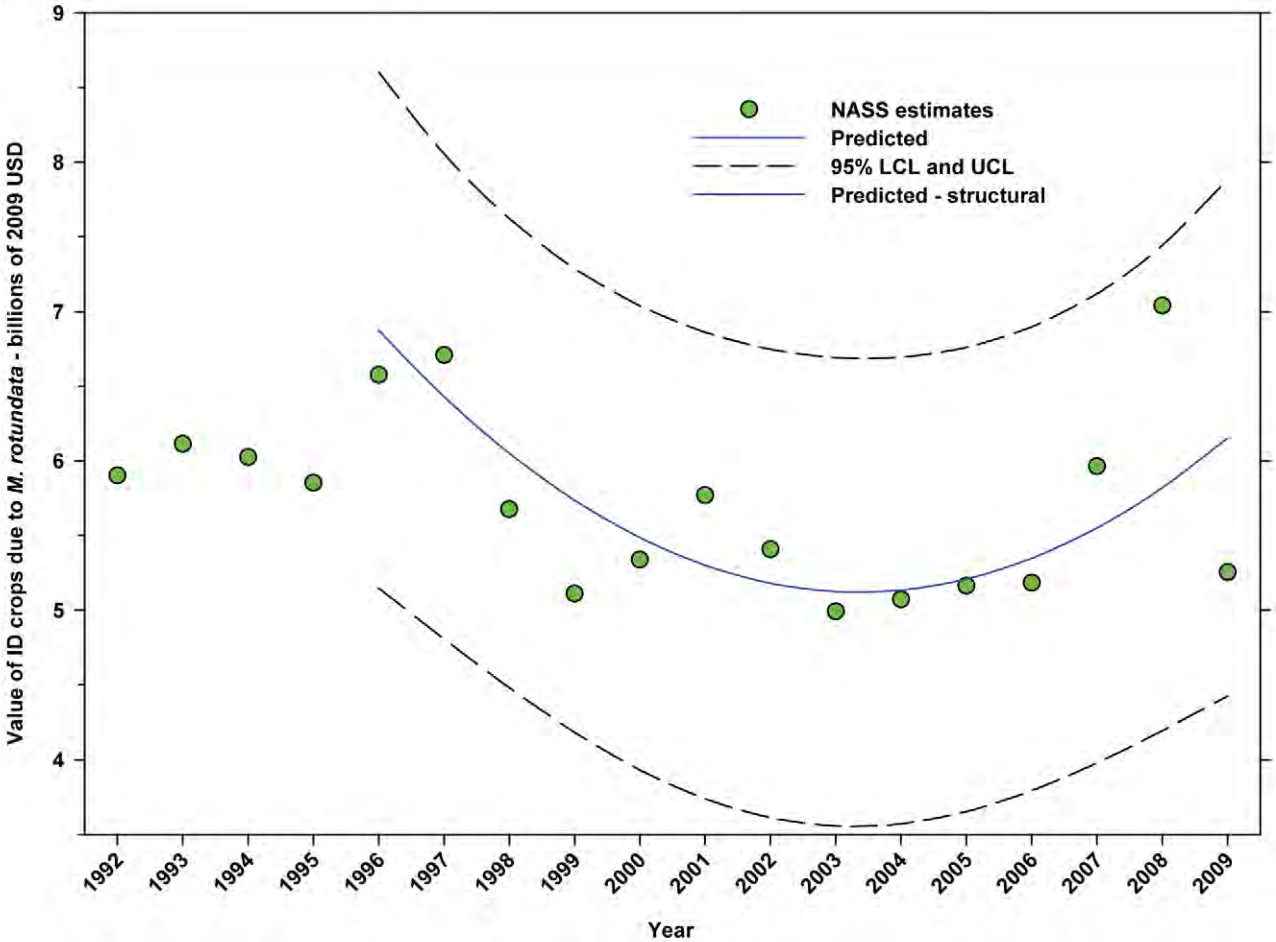

Figure 23. Value of indirectly dependent crops attributed to alfalfa leafcutter bees (*M. rotundata*). Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = indirectly dependent.
doi:10.1371/journal.pone.0037235.g023

As with other non-*Apis* managed pollinators, supply questions remain unanswered.

If production of alfalfa leafcutter bees could be increased, they may increase their contribution to alfalfa seed production and possibly other crops [155–157]. However, leafcutter bee production is hampered by a number of parasites and pathogens, production is difficult to sustain in the US [158,159] and reserve capacity in Canada, the primary source of leafcutter bees for US alfalfa seed growers, is not known. The other commercial alfalfa seed pollinator, *N. melanderi*, requires conditions that would be expensive to duplicate outside of the Pacific Northwest.

If losses extended to other insect pollinators, grower options are very limited. A recent study valued insect pollination for deciduous fruit tree crops in South Africa as equal to the change in net income that growers would receive if insect pollinators were replaced by other means - the replacement cost method [160]. Substituting pollen dusting and hand pollination for insect pollinators was found to be effective, albeit more expensive. Replacement costs using these methods are sensitive to crop values and local labor rates, making them more or less attractive for different cropping systems and different countries. In addition, it may not be possible to collect and distribute pollen from some crops in the manner used for deciduous fruit trees.

Clearly, markets would adjust to a loss of honey bees and other insect pollinators; however, the above discussion suggests that the nature of those adjustments and the time-scale over which they would occur are difficult to predict and would vary from crop to crop. The use of managed non-*Apis* pollinators may be possible for some crops but not for others; and where such use is possible, it may take considerable time to develop reliable, cost-effective management systems and sufficient populations. Further, there is no guarantee that the new equilibrium would include either the same diversity and abundance of insect-pollinated crops or the same level of affordability for those products. In brief, marketplace options for pollinators are simply not equivalent to grower options for most other inputs or most commodities in general. Hence, a precipitous loss of pollinators would likely have a major impact on production and prices, at least in the near term, with crops grown in large monocultures most seriously affected [161].

The concern over the sustainable production of insect-pollinated crops arises in part from the fact that the total number of colonies in the US has trended downward since 1947 [52]. This trend has continued in recent years. The number of colonies declined from 3.53 million in 1989 (five years after detection of the tracheal mite *A. woodi* in the US [162] and two years after detection of *V. destructor* [163]) to 2.30 million in 2008, a decline of

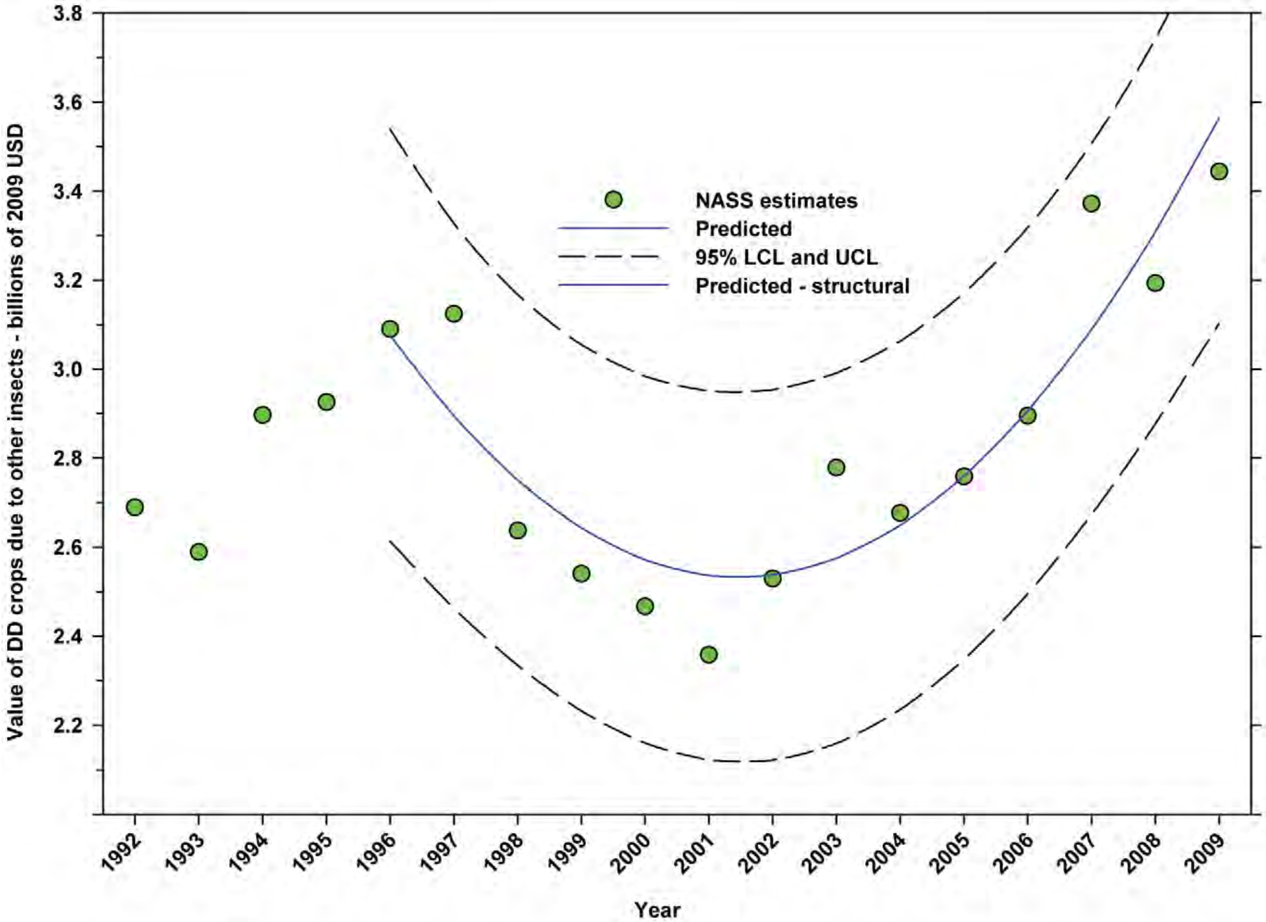

Figure 24. Value of directly dependent crops attributed to other insects. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. DD = directly dependent.
doi:10.1371/journal.pone.0037235.g024

34.81% (Fig. S1 in Text S4); however, there were increases to 2.46 and 2.68 million colonies in 2009 and 2010, respectively. Despite those increases, the overall trajectory maintains a downward trend; and the numbers are already well below the number required to satisfy estimated number of recommended colony rentals (8.98 million in 2009 not including colonies for cotton lint, and 30.40 million including colonies for cotton lint (see Fig. S2 and Text S4 for discussion of underestimates of the contributions of wild bees). Interestingly, the long-term downward trend was underway well before the arrival of parasitic mites CCD. This suggests that the downward trend may be independent of recent, large losses being reported with the primary impact of those losses being an increase in operating costs for beekeepers and pollination rental fees [164–169].

Regardless of the cause, the decline in colony numbers does not yet appear to have reduced the production or yield of insect-pollinated crops. The cultivated area of DD crops increased from 1992 through 2004, declining slightly thereafter (Fig. S3 and Text S4). That might suggest a response by growers to maintain production in the face of a decline in the honey bee population [58,64]; however, other data do not support that hypothesis. The production of DD crops actually increased between 1992 and 2003, after which there was a slight downward trend (Fig. S4 and Text S4). The most rapid growth occurred as the number of colonies declined most rapidly. Additionally, the aggregate yield of DD crops remained steady from 1992 through 2009 despite a declining number of colonies (Fig. S5 and Text S4). These findings suggest that the decline of managed honey bee colonies has not yet resulted in a pollinator shortage. However, aggregate data mask variation among crops; and shortages may disproportionately affect crops with differing degrees of dependency on insect pollinators [64]; therefore, this conclusion should be considered tentative pending further analysis.

Honey bees provide the major share of crop pollination in the US, especially in large cropping systems. There are several reasons for this. Honey bees are an established commodity that fit into a familiar business model in which producers purchase inputs rather than relying on natural ecosystem services [170]. In addition, each colony provides thousands of pollinators; colony management is well developed, so numbers have been adequate and reliable; honey bees are available any time crops are in bloom; honey bees pollinate a large number of crops; honey bees have extended foraging ranges making them suitable for large monocultures; foragers exhibit floral constancy on any single trip to the field; and colonies are easily transported by truck.

While those same factors support a continuing and prominent role for honey bees, the increase in colony rental fees and concerns over possible shortages have provided growers with considerable

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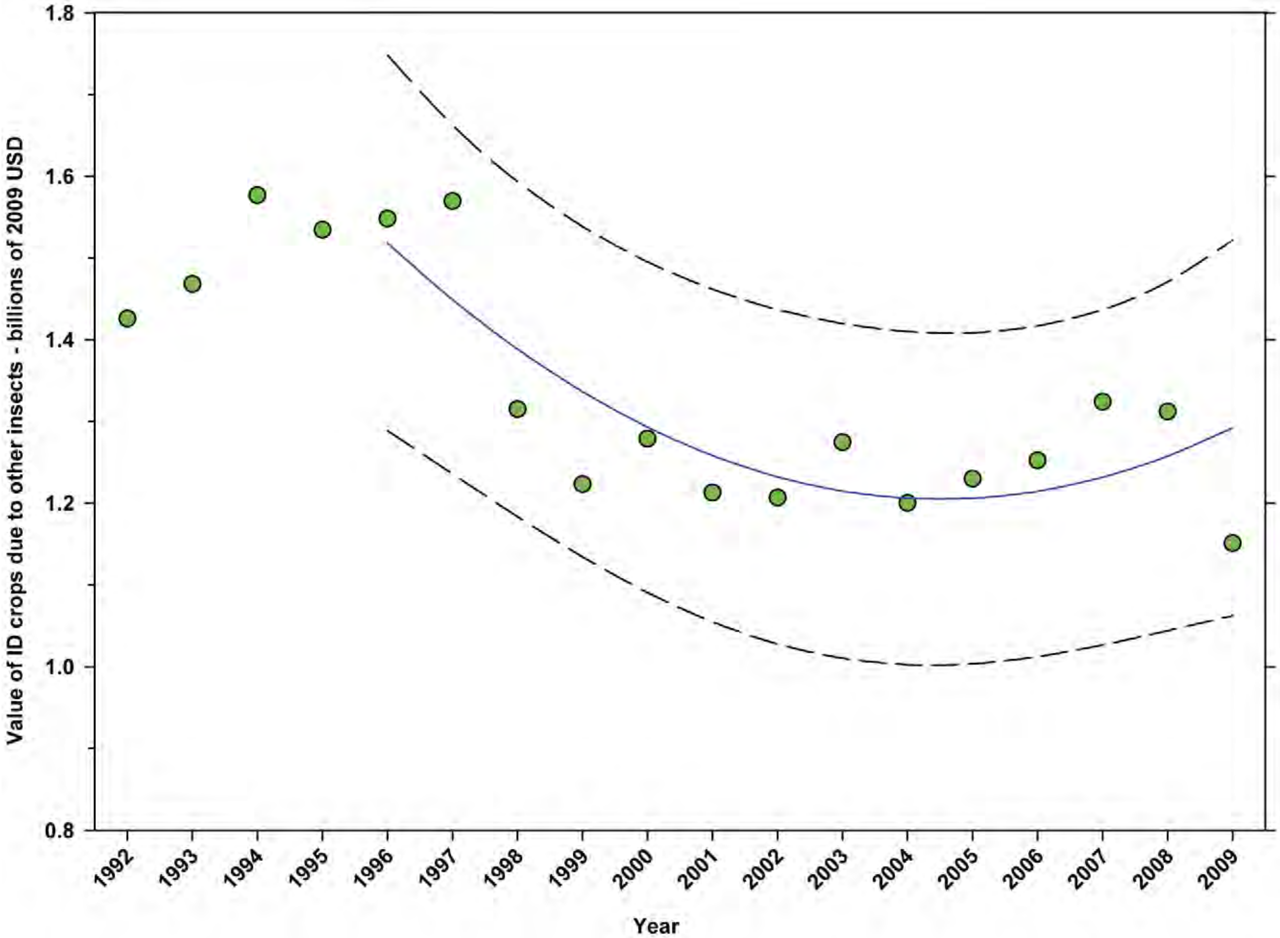

Figure 25. Value of indirectly dependent crops attributed to other insects. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model. ID = indirectly dependent.
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impetus to diversify their pollinator portfolio. Many growers are experimenting with bumble bees; interest in protecting and enhancing populations of native bees has increased; and recently, one major almond grower established a program to develop a population of several million *O. lignaria*. From a systems perspective, pollinator diversification is highly desirable because it provides redundancy in a critical component of all pollinator-dependent cropping systems, thereby increasing system reliability. To maintain its competitive position, the beekeeping industry will need to develop a sustainable, market-based system of bee breeding and colony management that can continue to provide an adequate and reliable supply of high quality, healthy pollinators at competitive prices.

Supporting Information

Text S1 Alfalfa production: supporting text for "Insect pollinated crops, insect pollinators and US agriculture: Trend analysis of aggregate data for the period 1992–2009."
(PDF)

Text S2 Individual crops for 2002 and 2007: supporting text for "Insect pollinated crops, insect pollinators and US agriculture: Trend analysis of aggregate data for the period 1992–2009."
(PDF)

Text S3 Update for individual crops for 2010: supporting text for "Insect pollinated crops, insect pollinators and US agriculture: Trend analysis of aggregate data for the period 1992–2009."
(PDF)

Text S4 Decline in number of honey bee colonies and the pollinator shortage: supporting text for "Insect pollinated crops, insect pollinators and US agriculture: Trend analysis of aggregate data for the period 1992–2009."
(PDF)

Figure S1 Number of managed colonies of honey bees in the United States. Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model.
(TIF)

Figure S2 Number of managed colonies required to meet current recommendations for pollination. Data includes recommendations for all crops except cotton lint.

Predicted values (blue) include adjustments for serial autocorrelation and are the same as the predicted – structural values (also blue) based solely on the structural elements of the model.
(TIF)

Figure S3 Predicted values for the number of managed colonies and hectares of directly dependent crops. DD = directly dependent.
(TIF)

Figure S4 Predicted values for the number of managed colonies and tonnes of directly dependent crops. DD = directly dependent.
(TIF)

Figure S5 Predicted values for the number of managed colonies and yield of directly dependent crops. DD = directly dependent.
(TIF)

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Author Contributions

Conceived and designed the experiments: NWC. Analyzed the data: NWC. Contributed reagents/materials/analysis tools: NWC. Wrote the paper: NWC.

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Research Article

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Investigating the mode of action of sulfoxaflor: a fourth-generation neonicotinoid

Penny Cutler,[a] Russell Slater,[b] Andrew JF Edmunds,[c] Peter Maienfisch,[c] Roger G Hall,[c] Fergus GP Earley,[a] Thomas Pitterna,[c] Sitaram Pal,[d] Verity-Laura Paul,[b] Jim Goodchild,[a] Melissa Blacker,[a] Leonhard Hagmann[c] and Andrew J Crossthwaite[a*]

Abstract

BACKGROUND: The precise mode of action of sulfoxaflor, a new nicotinic acetylcholine receptor-modulating insecticide, is unclear. A detailed understanding of the mode of action, especially in relation to the neonicotinoids, is essential for recommending effective pest management practices.

RESULTS: Radiolabel binding experiments using a tritiated analogue of sulfoxaflor ([^{3}H]-methyl-SFX) performed on membranes from *Myzus persicae* demonstrate that sulfoxaflor interacts specifically with the high-affinity imidacloprid binding site present in a subpopulation of the total nAChR pool. In competition studies, imidacloprid-like neonicotinoids displace [^{3}H]-methyl-SFX at pM concentrations. The effects of sulfoxaflor on the exposed aphid nervous system *in situ* are analogous to those of imidacloprid and nitenpyram, and finally the high-affinity sulfoxaflor binding site is absent in a *Myzus persicae* strain (clone FRC) possessing a single amino acid point mutation (R81T) in the β-nAChR, a region critical for neonicotinoid interaction.

CONCLUSION: The nicotinic acetylcholine receptor pharmacological profile of sulfoxaflor in aphids is consistent with that of imidacloprid. Additionally, the insecticidal activity of sulfoxaflor and the current commercialised neonicotinoids is affected by the point mutation in FRC *Myzus persicae*. Therefore, it is suggested that sulfoxalfor be considered a neonicotinoid, and that this be taken into account when recommending insecticide rotation partnering for effective resistance management programmes.

Keywords: Imidacloprid; resistance; pest management; nicotinic acetylcholine receptor; *Myzus persicae*; radiolabel

1 INTRODUCTION

A common theme for the most successful systemic insecticides targeting sucking pest control is their ability to disrupt acetylcholine (ACh) neurotransmitter signalling. The organophosphates and carbamates, both acetylcholine esterase (ACh-esterase) inhibitors, were the dominant class for much of the latter half of the twentieth century. However, owing to their weak selectivity for the insect ACh-esterase over the mammalian form, they have been gradually replaced by the safer neonicotinoids. All neonicotinoids share the same mode of action – modulation of the nicotinic acetylcholine receptor (nAChR).[1] Neonicotinoids are highly selective for the insect nAChR over the mammalian form, a feature imparting their improved safety profile.[2–4] Imidacloprid (IMD) (**1**) was the first neonicotinoid, launched over 20 years ago, with seven now commercialised for crop protection use (Fig. 1). The neonicotinoids can be subdivided on the basis of their chemical structure: the first-generation chloro-pyridyls [imidacloprid (**1**), nitenpyram (**2**), acetamiprid (**3**) and thiacloprid (**4**)], the second-generation chlorothiazolyls [thiamethoxam (**5**) and clothianidin (**6**)] and finally the third-generation furanyls [dinotefuran (**7**)].[5]

The total annual combined global sales for the neonicotinoids is in excess of $2.4 billion (>20% of the conventional insecticide market in 2009),[6] and, owing to their widespread use, pest resistance to neonicotinoids is an increasing issue.[7–9] The minimisation of resistant insect selection pressure requires careful pest management practices, through knowledge of metabolic cross-resistance risk and, importantly, insecticidal mode of action.

The discovery of novel pesticides with enhanced features over commercialised chemistry, such as a novel mode of action, is the mainstay for research and development within the agchem industry. Sulfoxaflor (SFX) (**8**) (Fig. 1), a new insecticide from Dow Agrosciences that is due for first sales in 2012, is effective against a range of sucking insects, with a pest spectrum highly analogous to that of the neonicotinoids.[10,11] A potential attractive attribute of sulfoxaflor over the current neonicotinoids is its ability

* Correspondence to: Andrew J Crossthwaite, Syngenta Crop Protection, Biological Sciences, Jealott's Hill International Research Centre, Bracknell RG42 6EY, UK. E-mail: andrew.crossthwaite@syngenta.com

a Syngenta Crop Protection, Biological Sciences, Jealott's Hill International Research Centre, Bracknell, UK

b Syngenta Crop Protection, Biological Sciences, Stein, Switzerland

c Syngenta Crop Protection, Insecticide Chemistry, Stein, Switzerland

d Syngenta Crop Protection, Insecticide Chemistry, Corlim, Ilhas, Goa, India

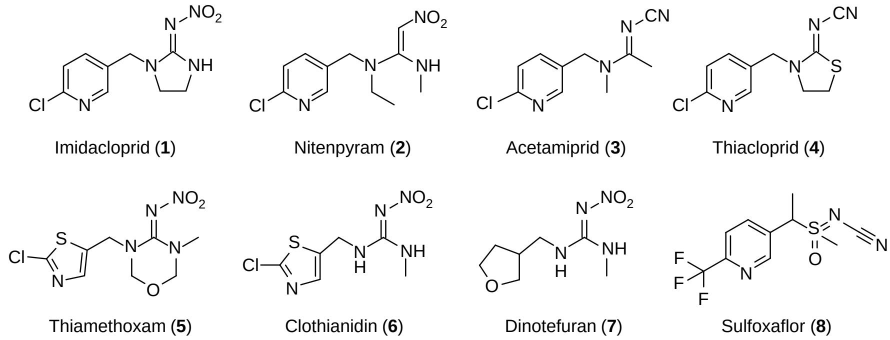


Figure 1. Structures of commercial neonicotinoids.

to control certain sucking pests that have developed a metabolic-based resistance to neonicotinoids.[10] However, resistance to neonicotinoid insecticides is not necessarily solely based on altered metabolism, and a number of other mechanisms give rise to resistance, including target-site alterations.[8] Therefore, having a detailed understanding of the mode of action of sulfoxaflor, especially in relation to the neonicotinoids, is essential in recommending insecticide rotation partnering for effective resistance management programmes.

Sulfoxaflor is thought to mediate its insecticidal effects through an interaction with the nAChR, although the mechanism of action is not clear. Studies on stick insects (*Carausius morosus*) have shown the presence of a high-affinity interaction at the nAChR; however, so far, in aphids (a principal pest target) there is little understanding of sulfoxaflor pharmacology. Indeed, displacement of [^{3}H]-IMD (tritiated imidacloprid, labelled at the methylene carbon between the pyridine and imidazolidine ring sytems (see reference 20) by sulfoxaflor in membranes prepared from aphids is relatively weak, especially given sulfoxaflor's potent aphicidal toxicity.[10,12,13] On this basis, combined with sulfoxaflor's structural differences to the current commercialised neonicotinoids, it has been suggested that sulfoxaflor has a unique interaction at the nAChR.[10,12,14] Studies with a radiolabelled version of sulfoxaflor have been acknowledged as required to allow a deeper analysis of sulfoxaflor's mode of action.[12] In the present study, such a strategy was adopted, utilising a custom synthesis of tritiated methyl-sulfoxaflor ([^{3}H]-methyl-SFX), a close analogue of sulfoxaflor. This biochemical approach, combined with aphid electrophysiology and whole-insect bioassays, provides compelling evidence that sulfoxaflor should be considered a neonicotinoid, the first member of the fourth generation, from the sulphoximine chemical class. Most importantly, with the discovery of sulfoxaflor, the sulfoximine subclass has been added to the neonicotinoid class, possessing a novel and innovative pharmacophore – the *N*-cyanosulfoximine pharmacophore.[2,3,5]

2 EXPERIMENTAL METHODS

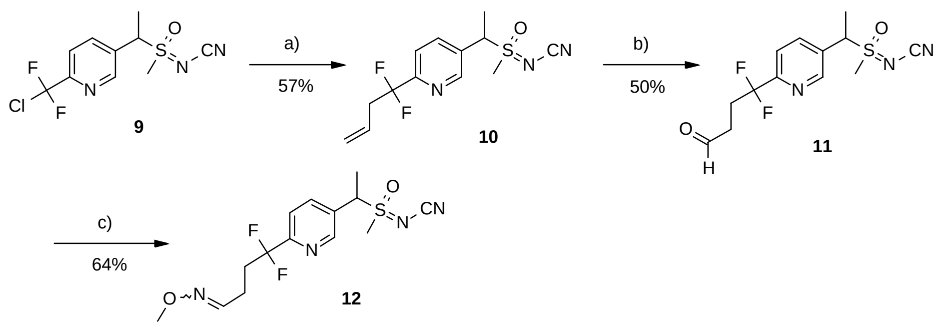
2.1 Chemistry synthesis

The compounds required for this study were synthesised according to Schemes 1, 2 and 3.

In Scheme 1, compound **9**[15] was converted to **10** by a radical allylation. Wacker oxidation of the vinyl group led to the aldehyde highly regioselectively. This result was very surprising, as Wacker oxidation on a very similar substrate in the present authors' labs had previously led to a methyl ketone.[16] The aldehyde **11** could smoothly be converted to an inseparable 1:1 mixture of the *syn*- and *anti*-methyl oximes.

In Scheme 2, the cyano group of sulfoxaflor could be converted to the trifluoroacetamide derivative **13** according to the method of Okamura and Bolm.[17] This was then readily hydrolysed to **14**, which could be subsequently electrophilically nitrated to yield compound **15**. Deprotonation of sulfoxaflor (**8**) yielded an anion that could be quenched with methyl iodide to yield methyl-sulfoxaflor (methyl-SFX) (**16**), or an electrophilic fluorinating agent to give a separable mixture of the diastereoisomers **18** and **19** [the absolute stereochemistry shown for **18** and **19** will be the subject of a future publication; it suffices to say here that the first eluted isomer from chromatography (**18**) was the one used in the present study]. Further deprotonation, and quenching of the resultant anion of dimethyl-sulfoxaflor with methyl iodide, yielded compound **17**. Careful hydrolysis of the cyano moiety of sulfoxaflor enabled isolation of the urea derivative **20**.

In Scheme 3, the sulphoxide derivative **25** was prepared using methods analogous to those previously described.[18] This was



Scheme 1. Reagents and conditions: (a) $CH_2{=}CHCH_2Sn(n\text{-}Bu)_3$/AIBN/trifluorotoluene, 90 °C; (b) $PdCl_2/CuCl_2$, (cat)/O_2/DMF/H_2O, rt: (c) $NH_2OMe.HCl$/MeOH, rt.

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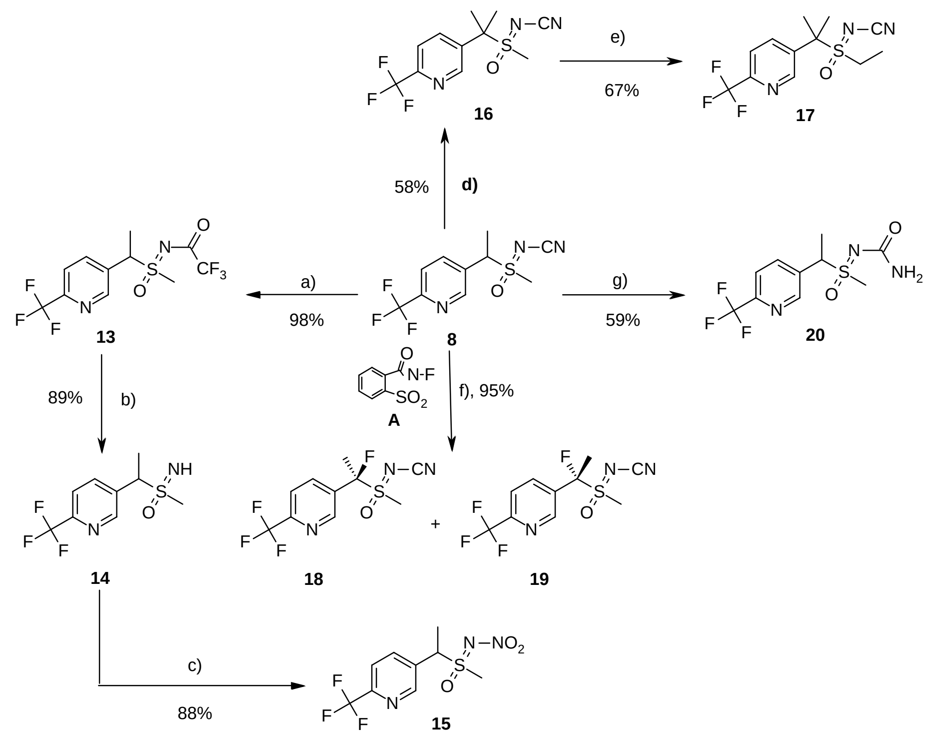
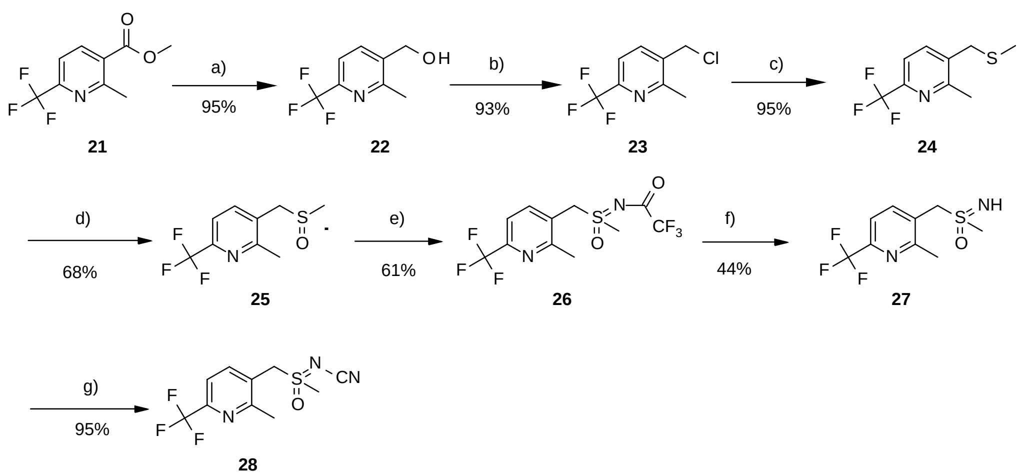
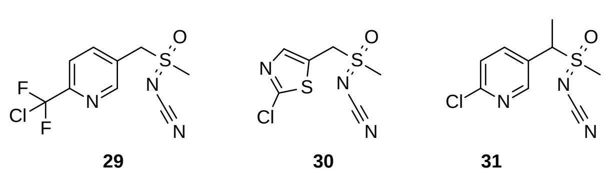


Scheme 2. Reagents and conditions: (a) $(CF_3CO)_2O$, CH_2Cl_2, rt; (b) K_2CO_3, MeOH, rt; (c) H_2SO_4, HNO_3, Ac_2O, CH_2Cl_2, rt; (d) LiN(i-Pr)2, THF, −78 °C, then add MeI; (e) LiN(i-Pr)$_2$, THF, −78 °C, then add MeI; (f) LiN(i-Pr)$_2$, THF, −78 °C, then add 2-fluoro-1,1-dioxo-1,2-benzothiazol-3-one (**A**); (g) KOH, H_2O, rt.



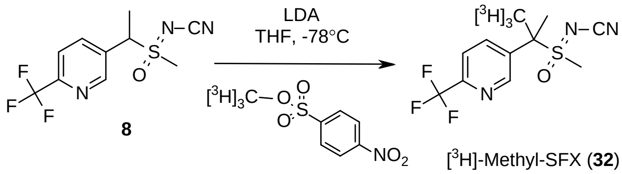
Scheme 3. Reagents and conditions: (a) DIBAL, THF, −78 °C; (b) $SOCl_2$, cat. DMF, toluene, rt; (c) NaSMe, DMF, rt; (d) *meta*-chloroperbenzoic acid, CH_2Cl_2, rt; (e) CF_3CONH_2, MgO, $PhI(OAc)_2$, $Rh_2(OAc)_2$ (cat.), CH_2Cl_2, rt; (f) K_2CO_3, MeOH, rt; (g) BrCN, Et_3N, DMAP, CH_2Cl_2, rt.

converted to the sulphoximine derivative **26** by rhodium-catalysed imination.[17] The trifluoroacyl group of **26** was readily cleaved by treatment with mild base, and the resultant **27** was cyanated with cyanogen bromide to give **28**. The remaining compounds (**29**, **30** and **31**) used in this study are known, or were prepared analogously to methods described below and in the literature.[19]



Radioligands. Having ascertained that methyl-SFX (**16**) showed good insecticidal activity in screens, and that it could be easily prepared by deprotonation of sulfoxaflor with subsequent quenching with a methyl electrophile equivalent, the authors chose to prepare [^{3}H]-methyl-SFX (**32**) as the radioligand for the present study. The radioligand was prepared as shown in Scheme 4.

All new compounds were characterised by standard spectroscopical and analytical methods. ^{1}H NMR (400 or 600 MHz) and ^{13}C NMR (150 or 101 MHz) spectra were recorded on Bruker Avance (400 MHz) and Varian Inova (600 MHz) spectrometers, using $CDCl_3$, $(CD_3)_2SO$, CD_3OD and CD_3CN as solvents and tetramethylsilane as internal standard. Chemical shifts were reported in ppm downfield from the standard ($\delta = 0.00$). LCMS



Scheme 4. This gave [^{3}H]-methyl-SFX (76 Ci mmol^{-1} or 2.81 TBq mmol^{-1}) with 99.7% purity. [^{3}H]-IMD (1.1 TBq mmol^{-1}), purity >95%, was synthesised in house, as previously described.[20]

spectra were obtained on a Waters ZQ ZMD mass spectrometer (single-quadripole mass spectrometer). Instrument parameters: ionisation method – electrospray; polarity – positive or negative ions; capillary – 3.80 kV; cone – 30.00 V; extractor – 3.00 V; source temperature – 150 °C; desolvation temperature – 350 °C; cone gas flow – OFF; desolvation gas flow – 600 L h^{-1}; mass range – 100–900 Da. Agilent HP 1100 HPLC: solvent degasser, binary pump, heated column compartment and diode-array detector. Phenomenex Gemini C18 column, 3 µm, 30 × 3 mm. Temperature 60 °C. DAD wavelength range 200–500 nm. Solvent gradient: A = H_2O + 5% MeOH + 0.05% HCOOH; B = acetonitrile + 0.05% HCOOH, flow 1.70 mL min^{-1}. Gradient 100:0 (A:B) at 0 min, 0:100 at 2.0 min, 0:100 at 2.8 min, 100:0 at 2.9 min and 100:0 at 3.0 min. Accurate mass data were collected on an Orbitrap Velos mass spectrometer at 30 000 resolution using atmospheric pressure chemical ionisation operating in the positive ion mode (APCI$^+$). Melting points were determined in open-end capillary tubes on a Büchi 530 melting point apparatus and were uncorrected. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated plates. Preparative flash chromatography was performed using silica gel 60 (40–63 µm; E Merck). Unless otherwise stated, all reactions were carried out under anhydrous conditions in an inert atmosphere (nitrogen or argon) with dry solvents. All reagents were purchased from commercial suppliers and used without further purification.

[{1-[6-(1,1-Difluorobut-3-en-1-yl)pyridin-3-yl]ethyl}(methyl)oxido-λ^6-sulfanylidene] cyanamide (**10**). A solution of [(1-{6-[chloro(difluoro)methyl]pyridin-3-yl}ethyl)(methyl)oxido-λ^6-sulfanylidene] cyanamide (**9**) (290 mg, 0.99 mmol[15]) in 10 mL of trifluorotoluene) was degassed with nitrogen and treated with azo-*bis*-(isobutyronitrile) (26 mg, 0.20 mmol) and allyl tri-*n*-butyl tin (660 mg, 2.00 mmol), and the reaction mixture was warmed to 90 °C. After 5 h, a further 26 mg of AIBN was added, and heating was continued for a further 18 h at 90 °C. LCMS analysis after this time showed reaction completion. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography, eluting with ethyl acetate:heptanes 3:1 to 1:1, to give the title compound (170 mg, 57%) as pale crystals, mp 61–62 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.97 (3H, d, J = 7.3 Hz), 3.05 and 3.10 (3H, s), 3.04–3.14 (2H, m), 4.70 (1H, q, J = 7.3 Hz), 5.16–5.21 (2H, m), 5.71–5.78 (1H, m), 7.71 (1H, d, J = 8.3 Hz), 7.99 (1H, dd, J = 8.3, 2.7 Hz), 8.71 (1H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 13.8, 37.7 and 38.1, 40.7 (J_t = 29 Hz), 64.0, 111.7 and 111.9, 120.1 (J_t = 240 Hz), 120.6, 121.0, 128.3, 128.7 and 128.8, 137.9 and 138.0, 150.0 and 150.1, 156.3 (J_t = 31 Hz).

LCMS: retention time 1.81 min. ES-API, Scan, ESI Pos: 300 (M + H)$^+$; 276. HRMS (APCI$^+$) m/z: calculated for ($C_{13}H_{15}F_2N_3OS$ + H)$^+$: 300.09767; found: 300.09854.

[{1-[6-(1,1-Difluoro-4-oxobutyl)pyridin-3-yl]ethyl}(methyl)oxido-λ^6-sulfanylidene] cyanamide (**11**). Palladium(II) chloride (142 mg, 0.80 mmol) and copper(II) chloride (537 mg, 4.01 mmol) were dissolved in 100 mL of a mixture of DMF:H_2O 7:1, and stirred at room temperature under an oxygen atmosphere for 1 h. A solution of **10** (1.20 g, 4.01 mmol) in 5 mL of DMF was added to the reaction, and stirring was continued for 48 h at room temperature. The reaction was quenched by adding a saturated solution of $NaHCO_3$ and extracted with dichloromethane, dried over sodium sulphate and concentrated *in vacuo*. Flash chromatography (ethyl acetate/heptanes = 75:25) afforded the title product (632 mg, 50%) as a colourless glass.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.96 (3H, d, J = 7.1 Hz), 2.60–2.71 (4H, m), 3.08 and 3.13 (3H, s), 3.04–3.14 (2H, m), 4.71 (1H, q, J = 7.1 Hz), 7.74 (1H, d, J = 8.3 Hz), 8.00 (1H, dd, J = 8.3, 2.7 Hz), 8.70 (1H, s), 9.77 (1H, s).

LCMS: retention time 0.63 min. ES-API, Scan, ESI Pos: 316 (M + H)$^+$; 147, 115. HRMS (APCI$^+$) m/z: calculated for ($C_{13}H_{15}O_2SF_2N_3$ + H)$^+$: 316.09258; found: 316.09290.

[(1-{6-[(4E,Z)-1,1-Difluoro-4-(methoxyimino)butyl]pyridin-3-yl}ethyl)(methyl)oxido-λ^6-sulfanylidene] cyanamide (**12**). A stirred solution of **11** (200 mg, 0.63 mmol) in 10 mL of MeOH was treated with *O*-methyl-hydroxylamine hydrochloride (88 mg, 1.06 mmol) and pyridine (170 mg, 1.30 mmol). The reaction was stirred at room temperature for 3 h, at which time the reaction was shown by LCMS to be complete. The reaction mixture was diluted with water, extracted with ethyl acetate, dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with ethyl acetate/heptanes 75:25, to 100% to yield 140 mg (64%) of the title compound (ca 1:1 isomer mixture) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.97 (3H, d, J = 7.3 Hz), 2.40–2.60 (4H, m), 3.07 and 3.12 (3H, s), 3.77 and 3.83 (3H, s), 4.71 (1H, q, J = 7.3 Hz), 6.63 and 7.35 (1H, m), 7.75 (1H, d, J = 8.3 Hz), 8.00 (1H, dd, J = 8.3, 2.7 Hz), 8.70 (1H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 13.8, 18.8 and 22.6, 32.6 (J_t = 30 Hz) and 32.8 (J_t = 30 Hz), 37.7 and 38.2, 61.2 and 61.6, 63.9, 111.6 and 111.8, 120.4, 120.6 (J_t = 247 Hz), 128.9 and 129, 138.1, 148.4 and 149.0, 150.1, 156.1 (J_t = 29 Hz).

LCMS: retention time 0.78 min. ES-API, Scan, ESI Pos: 345 (M + H)$^+$. HRMS (APCI$^+$) m/z: calculated for ($C_{14}H_{18}O_2N_4F_2S$ + H)$^+$: 345.11913; found: 345.11926.

2,2,2-Trifluoro-N-[methyl(oxido){1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}-λ^6-sulfanylidene] acetamide (**13**). This compound was prepared by modified procedures to those previously described.[21] A suspension of **8** (4.0 g, 13.7 mmol) in 40 mL of dichloromethane was stirred at room temperature and treated with trifluoroacetic acid anhydride (2.94 g, 13.8 mmol). After stirring for 1 h, the reaction mixture had become a clear solution, and TLC analysis showed reaction completion. The reaction mixture was concentrated *in vacuo* to give the title compound as a yellow amorphous solid (4.77 g, 100%) that was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.99 (3H, d, J = 7.0 Hz), 3.31 (3H, s), 4.88 (1H, q, J = 7.0 Hz), 7.79 (1H, d, J = 8.1 Hz), 8.07 (1H, dd, J = 8.2, 2.0 Hz), 8.75 (1H, s).

LCMS: retention time 1.65 min. ES-API, Scan, ESI Pos: 349 (M + H)$^+$, 215, 174.

5-[1-(S-Methylsulfonimidoyl)ethyl]-2-(trifluoromethyl)pyridine (**14**). This compound was prepared by modified procedures to those previously described.[15] A solution of **13** (4.70 g, 13.5 mmol) in 60 mL of methanol was treated with potassium carbonate (2.27 g, 16.5 mmol) at room temperature. LCMS analysis after 1 h showed reaction completion. The reaction mixture was concentrated *in vacuo* and filtered through silica gel, eluting with

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t-butyl methyl ether/acetone 1:1, to give the title compound (3.03 g, 89%) as a yellow resin.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm, 1:1 mixture of diastereoisomers: 1.84 and 1.87 (3H, d, $J = 7.0$ Hz), 2.41 (1H, br s), 2.88 and 2.91 (3H, s), 4.30–4.44 (1H, m), 7.75 (1H, d, $J = 8.1$ Hz), 8.05 (1H, m), 8.75 (1H, s).

LCMS: retention time 1.04 min. ES-API, Scan, ESI Pos: 253 (M + H)$^+$, 215, 174.

5-[1-(S-Methyl-N-nitrosulfonimidoyl)ethyl]-2-(trifluoromethyl)pyridine (**15**). This compound was prepared by modified procedures to those previously described.[15,21] A solution of **14** (520 mg, 2.0 mmol) in 10 mL of dichloromethane was cooled to 0 °C and treated with fuming nitric acid (126 mg, 2.0 mmol). The milky solution was then treated with concentrated sulphuric acid (40 mg, 0.4 mmol) and 3.5 mL of acetic acid anhydride. TLC analysis after 30 min showed reaction completion. The reaction mixture was diluted with water and carefully neutralised with aqueous $NaHCO_3$, extracted with dichloromethane, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with ethyl acetate/heptanes 5:1, to give the title compound (517 mg, 88%) as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) 1:1 mixture of diastereoisomers, δ ppm: 2.01 and 2.05 (3H, d, $J = 7.0$ Hz), 3.24 and 3.29 (3H, s), 3.28 (3H, s), 4.96 and 5.09 (1H, q, $J = 7.0$ Hz), 7.82 and 7.83 (1H, d, $J = 4.4$ Hz), 8.10 (1H, dd, $J = 8.1, 2.0$ Hz), 8.11 and 8.13 (1H, dd, $J = 8.1, 2.0$ Hz), 8.83 and 8.84 (1H, d, $J = 2.0$ Hz).

LCMS: retention time 1.39 min. ES-API, Scan, ESI Pos: 298 (M + H)$^+$, 215, 174.

1-[Methyl(oxido){1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}-λ^6-sulfanylidene]urea (**20**). A solution of sulfoxaflor (**8**, 100 mg[18]) in 4 mL of methanol/water 1:1 was treated with pulverised potassium hydroxide (19 mg, 0.343 mmol), and the suspension was stirred at room temperature. After 12 h the reaction mixture was heated to 50 °C for a further 2 h, and then concentrated *in vacuo*. The residue was dissolved in water and extracted with ethyl acetate, dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography, eluting with *t*-butyl methyl ether/acetone 7:3 + 1% triethylamine, gave the title compound **20**, a 1:1 mixture of diastereoisomers, as a colourless amorphous solid (60 mg, 59%).

^{1}H NMR (400 MHz, CD_3CN) δ ppm: 1.81 and 1.84 (3H, d, $J = 7.0$ Hz), 2.15 (2H, br s), 3.12 and 3.15 (3H, s), 4.80–4.92 (1H, m), 7.82 (1H, dd, $J = 8.6, 3.8$ Hz), 8.13 (1H, m), 8.32 and 8.35 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 14.6, 37.1, 60.9, 120.7 ($J_q = 2.7$ Hz), 121.4 ($J_q = 274$ Hz), 132.3, 138.6, 149.1 ($J_q = 35$ Hz), 151.0, 161.0.

LCMS: retention time 0.59 min. ES-API, Scan, ESI Pos: 296 (M + H)$^+$. HRMS (APCI$^+$) *m/z*: calculated for $(C_{10}H_{12}O_2F_3N_3S + H)^+$: 296.06751; found: 296.06805.

[Methyl(oxido){2-[6-(trifluoromethyl)pyridin-3-yl]propan-2-yl}-λ^6-sulfanylidene]cyanamide (**16**). A solution of sulfoxaflor (**8**, 4.0 g, 13.7 mmol[18]) in 40 mL of anhydrous THF was cooled to −60 °C and treated with lithium diisopropyl amide (8 mL of a 1.8 M solution in THF, 14.4 mmol) and stirred for 1 h at this temperature. The yellow solution was then treated with methyl iodide (2.16 g, 15.1 mmol), and the reaction mixture was allowed to warm to room temperature, where LCMS showed reaction completion. The reaction mixture was diluted with *t*-butyl methyl ether and quenched with 10 mL of 1N HCl. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography, eluting with *t*-butyl methyl ether/acetone 4:1, gave 2.32 g (58%) of the title product as white crystals, mp 89–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.08 (6H, s), 2.98 (3H, s), 7.81 (1H, dd, $J = 8.4, 2.6$ Hz), 8.22 (1H, dd, $J = 8.4, 2.6$ Hz), 8.97 (1H, d, $J = 2.6$ Hz); ^{13}C NMR [101 MHz, $CDCl_3$ + 10% $(CD_3)_2SO$] δ ppm: 21.5, 26.1, 34.7, 67.2, 111.3, 119.6, 120.7 ($J_q = 277$ Hz), 133.3, 137.8, 148.1 ($J_q = 35$ Hz), 149.2.

LCMS: retention time 0.73 min. ES-API, Scan, ESI Pos: 292 (M + H)$^+$, 188. HRMS (APCI$^+$) *m/z*: calculated for $(C_{11}H_{12}ON_3F_3S + H)^+$: 292.07259; found: 292.07230.

[Ethyl(oxido){2-[6-(trifluoromethyl)pyridin-3-yl]propan-2-yl}-λ^6-sulfanylidene]cyanamide (**17**). A solution of **16** (200 mg, 0.69 mmol) in 5 mL of anhydrous THF was cooled to −60 °C and treated with lithium diisopropyl amide (0.41 mL of a 1.8 M solution in THF, 0.76 mmol) and stirred for 1 h at this temperature. The mixture was then treated with methyl iodide (104 mg, 0.76 mmol), and the reaction mixture was allowed to warm to room temperature, where LCMS showed reaction completion. The mixture was diluted with *t*-butyl methyl ether and quenched with 10 mL of 1N HCl. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography, eluting with *t*-butyl methyl ether/acetone 7:3, gave 140 mg (67%) of the title product as an oil.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm: 1.44 (3H, t, $J = 7.4$ Hz), 2.10 (6H, s), 2.78–2.97 (1H, m), 3.00–3.16 (1H, m), 7.81 (1H, d, $J = 8.4$ Hz), 8.23 (1H, d, $J = 8.4$ Hz), 8.97 (1H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 5.5, 22.5, 29.7, 42.8, 68.7, 112.1, 120.5, 121.0 ($J_q = 270$ Hz), 134.3, 138.2, 149.0, 149.1 ($J_q = 34$ Hz).

LCMS: retention time 0.77 min. ES-API, Scan, ESI Pos: 306 (M + H)$^+$, 188. HRMS (APCI$^+$) *m/z*: calculated for $(C_{12}H_{14}ON_3F_3S + H)^+$: 306.08824; found: 306.08844.

[{(1S)-1-Fluoro-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}(methyl)oxido-λ^6-sulfanylidene] cyanamide and [{(1R)-1-fluoro-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}(methyl)oxido-λ^6-sulfanylidene] cyanamide (**18** and **19**). A solution of sulfoxaflor (**8**, 200 mg, 0.69 mmol[18]) in 6 mL of anhydrous THF was cooled to −50 °C and treated with lithium diisopropyl amide (0.68 mL of a 1.8 M solution in THF, 1.23 mmol). The yellow solution was then treated with *N*-fluoro-*bis*-(phenylsulphonyl)-amine (408 mg, 1.27 mmol), and the reaction mixture was allowed to warm to room temperature, where LCMS showed reaction completion. The mixture was diluted with *t*-butyl methyl ether and quenched with 10 mL of 1N HCl. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography, eluting with *t*-butyl methyl ether/acetone 7:3, gave the first eluting product diastereoisomer (**18**, 89 mg, 44%) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.36 (3H, d, $J = 24$ Hz), 3.09 (3H, s), 7.87 (1H, d, $J = 8.23$ Hz), 8.15 (1H, dd, $J = 8.2, 2.4$ Hz), 8.99 (1H, d, $J = 2.4$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 20.4 ($J_d = 21$ Hz), 39.1, 106.4 ($J_d = 281$ Hz), 112.1, 120.4 ($J_{qui} = 2.5$ Hz), 121.3 ($J_q = 274$ Hz), 133.0 ($J_d = 21$ Hz), 136.0 ($J_d = 9$ Hz), 147.6 ($J_d = 9$ Hz), 151.6 ($J_q = 36$ Hz).

LCMS: retention time 1.38 min. ES-API, Scan, ESI Pos: 296 (M + H)$^+$, 233, 192. HRMS (APCI$^+$) *m/z*: calculated for $(C_{10}H_9F_4N_3OS + H)^+$: 296.04752; found: 296.04717.

Further elution gave the second diastereoisomer (**19**, 104 mg, 51%) as an amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.34 (d, $J = 24$ Hz, 3 H), 2.32 (s, 2 H), 3.18 (s, 3 H), 7.87 (d, $J = 8.4$ Hz, 1 H), 8.19 (dd, $J = 8.4$, 2.2 Hz, 1 H), 9.00 (d, $J = 2.2$ Hz, 1 H).

LCMS: retention time 1.36 min. ES-API, Scan, ESI Pos: 296 $(M + H)^+$, 233, 192. HRMS ($APCI^+$) *m/z*: calculated for $(C_{10}H_9F_4N_3OS + H)^+$: 296.04752; found: 296.04721.

[2-Methyl-6-(trifluoromethyl)-3-pyridyl]methanol compound (**22**). A solution of **21** (5.0 g, 21.4 mmol[22]) in anhydrous THF (30 mL) was treated dropwise at −78 °C with diisobutylaluminium hydride (36 mL, 1.9 M in toluene, 53.6 mmol). The reaction mixture was allowed to warm to room temperature, at which time TLC analysis showed reaction completion. The reaction mixture was carefully quenched with 2N aqueous HCl, extracted with ethyl acetate, dried over magnesium sulphate and concentrated *in vacuo*. This gave **22** as a yellow solid (3.9 g, 95%) that was used in the next step without further purification.

1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.80–2.09 (1H, m), 2.59 (3H, s), 4.81 (2H, s), 7.56 (1H, d, $J = 8.0$ Hz, 1 H), 7.93 (1H, d, $J = 8.0$ Hz).

3-(Chloromethyl)-2-methyl-6-(trifluoromethyl)pyridine (**23**). A solution of **22** (3.9 g, 20.4 mmol) in toluene (60 mL) containing 1 mL of DMF was treated carefully at room temperature with thionyl chloride (4.38 g, 40.8 mmol). The reaction mixture was stirred at room temperature until TLC analysis showed completion. The reaction mixture was quenched with water, extracted with ethyl acetate, dried over magnesium sulphate and concentrated *in vacuo*. This gave **23** as a yellow oil that was triturated with *n*-hexane to give 4.0 g (93%) of the title compound as pale yellow crystals, mp 39–40 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.72 (3H, s), 4.64 (2H, s), 7.54 (1H, d, $J = 8.0$ Hz), 7.82 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 21.8, 42.6, 118.2, 121.4 ($J_d = 274$ Hz), 134.2, 138.1, 147.2 ($J_q = 34$ Hz), 158.4.

2-Methyl-3-(methylsulfanylmethyl)-6-(trifluoromethyl)pyridine (**24**). Sodium methyl thiolate (4.65 g, 63.0 mmol) was dissolved in 50 mL of DMF and treated at room temperature with a solution of **23** (11.0 g, 52.5 mmol) (exothermic) in 30 mL of DMF. The reaction was complete, according to TLC analysis, after 1 h. The reaction mixture was diluted with *t*-butyl methyl ether and quenched with water. The organic phases were dried over magnesium sulphate, concentrated *in vacuo* and purified by flash chromatography, eluting with heptanes/ethyl acetate 6:1, to give 11.0 g (95%) of the product as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.05 (3H, s), 2.69 (3H, s), 3.72 (2H, s), 7.49 (1H, d, $J = 8.0$ Hz), 7.65 (1H, d, $J = 8.0$ Hz).

2-Methyl-3-(methylsulfinylmethyl)-6-(trifluoromethyl)pyridine (**25**). A solution of compound **24** (5.5 g, 24.86 mmol) in dichloromethane (50 mL) was treated dropwise with a solution of *m*-chloroperbenzoic acid (6.13 g, 24.86 mmol) at 0 °C. TLC after addition showed reaction completion (small amount of sulphone also formed). The reaction mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$, dried over magnesium sulphate and concentrated *in vacuo*. Purification by flash chromatography, eluting with ethyl acetate to ethyl acetate/5% methanol, gave the title product (4.0 g, 68%) as a white powder, mp 130–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.64 (3H, s), 2.72 (3H, s), 4.08 (1H, d, $J_{AB} = 12$ Hz), 4.04 (1H, d, $J_{AB} = 12$ Hz), 7.56 (1H, d, $J = 8.0$ Hz), 7.76 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 22.8, 38.6, 57.0, 118.2, 121.4 ($J_d = 275$ Hz), 128.0, 139.9, 147.5 ($J_q = 35$ Hz), 158.6.

*2,2,2-Trifluoro-*N*-(methyl{[2-methyl-6-(trifluoromethyl)pyridin-3-yl]methyl}oxido-λ^6-sulfanylidene)acetamide* (**26**). To a suspension of **25** (3.20 g, 13.5 mmol), trifluoroacetamide (3.05 g, 27.0 mmol), magnesium oxide (2.17 g, 53.95 mmol) and rhodium(II) acetate dimer (300 mg, 0.67 mmol, 5 mol%) in 70 mL of dichloromethane was added diacetoxy iodo-benzene (6.95 g, 21.6 mmol), and the mixture was stirred at room temperature until reaction completion. The mixture was diluted with dichloromethane, filtered over hyflo and concentrated *in vacuo*. Purification by flash chromatography, eluting with cyclohexane/ethyl acetate 2:1, afforded the title compound (4.60 g, 98%) as beige crystals, mp 106–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.80 (3H, s), 3.34 (3H, s), 4.77 (1H, d, $J_{AB} = 16$ Hz), 4.94 (1H, d, $J_{AB} = 16$ Hz), 7.63 (1H, d, $J = 8.0$ Hz), 7.89 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 22.8, 38.8, 56.1, 115.6 ($J_q = 286$ Hz), 118.4, 121.2 ($J_q = 275$ Hz), 123.1, 141.2, 149.0 ($J_q = 35$ Hz), 160.0, 164.2 ($J_q = 38$ Hz).

2-Methyl-3-[(S-methylsulfonimidoyl)methyl]-6-(trifluoromethyl)pyridine (**27**). A solution of **26** (4.60 g, 13.21 mmol) in methanol (150 mL) and potassium carbonate (5.48 g, 10.8 mmol) was stirred at room temperature until reaction completion. The reaction mixture was concentrated *in vacuo*, taken up in ethyl acetate, washed with water, dried over sodium sulphate and concentrated *in vacuo*. The crude product was filtered through silica gel, eluting with hexane/ethyl acetate 3:1, to give the title compound (3.10 g, 93%) as pale yellow crystals, mp 111–114 °C.

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ ppm: 2.69 (3H, s), 3.75 (3H, s), 5.44 (1H, d, $J_{AB} = 16.0$ Hz), 5.49 (1H, d, $J_{AB} = 16.0$ Hz), 5.89 (1H, br s), 7.87 (1H, d, $J = 8.0$ Hz), 8.17 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$ + 10% CD_3OD) δ ppm, selected data: 22.3, 40.1, 57.6, 118.4, 123.5, 142.1, 148.4 ($J_q = 35$ Hz).

LCMS: retention time 0.58 min. ES-API, Scan, ESI Pos: 253 $(M + H)^+$. HRMS ($APCI^+$) *m/z*: calculated for $(C_9H_{11}OF_3N_2S + H)^+$: 253.06169; found: 253.06180.

(Methyl{[2-methyl-6-(trifluoromethyl)pyridin-3-yl]methyl}oxido-λ^6-sulfanylidene) cyanamide (**28**). A solution of **27** (270 mg, 1.01 mmol) in methyl dichloride (10 mL) was treated with triethylamine (310 mg, 3.0 mmol), dimethyl amino pyridine (100 mg, 0.1 mmol) and cyanogen bromide (210 mg, 1.0 mmol) at 0 °C and stirred at room temperature until reaction completion. The reaction mixture was diluted with dichloromethane and washed successively with 2N HCl and saturated aqueous $NaHCO_3$, dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with dichloromethane/acetone 4:1, to give the product as an oil that could be recrystallised from hexane to yield the title compound (200 mg, 68%) as white crystals, mp 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.79 (3H, s), 3.24 (3H, s), 4.69 (1H, d, $J_{AB} = 16.0$ Hz), 4.79 (1H, d, $J_{AB} = 16.0$ Hz), 7.66 (1H, d, $J = 8.0$ Hz), 7.95 (1H, d, $J = 8.0$ Hz).

LCMS: retention time 1.30 min. ES-API, Scan, ESI Neg: 276 (M − H). HRMS ($APCI^+$) *m/z*: calculated for $(C_{10}H_{10}OF_3N_3S + H)^+$: 278.05694; found: 278.05685.

[^{3}H]-Methyl-SFX (**32**). The synthesis was carried out by Amersham Radiolabelling Service (GE Healthcare Life Sciences, Cardiff, UK). A solution of sulfoxaflor (**8**, 10 mg, 0.036 mmol) in 1 mL of anhydrous THF was cooled to −60 °C and treated with freshly prepared lithium diisopropyl amide (60 µL of a 1.25 M solution in THF, 0.08 mmol) and stirred at −60 °C for 30 min. [^{3}H]-Methyl nosylate (1 Ci) dissolved in 1 mL of THF was added at −60 °C, stirring at this temperature was continued for a further 15 min, and then the reaction mixture was allowed to warm to room temperature, stirred for a further 1 h and then quenched with 25 mL of ethanol. The reaction mixture was concentrated and purified by HPLC on an Ultrasphere ODS

column (250 × 9.6 mm), eluting with a H_2O/MeOH/Et_3N gradient system. Further purification was carried out on a Luna C18 column (250 × 9.6 mm), eluting with a H_2O/CH_3CN/TFA gradient system. The product was collected and concentrated *in vacuo*, and the residue was dissolved in ethanol (10 mL). The radiochemical purity of [^{3}H]-methyl-SFX (**32**) was shown by HPLC analysis [Luna C18 5 µm column (250 × 4.6 mm)] to be 99.7%. Mass spectrometry of the sample gave a spectrum consistent with the labelled compound (mass 297) and a specific activity of 76 Ci mmol^{-1}.

2.2 Materials

Formulated insecticides used in the *Myzus persicae* cross-resistance study were thiamethoxam (ACTARA 25WG; Syngenta Crop Protection), imidacloprid (CONFIDOR 20LS; Bayer CropScience), clothianidin (Dantotsu SG16; Sumitomo Chemical Co., Ltd), acetamiprid (Gazelle SG20; Nippon Soda Co., Ltd), thiacloprid (Alanto SC480; Bayer CropScience), nitenpyram (Bestguard SG10; Takeda) and dinotefuran (Starkle SG20; Mitsui Chemicals Agro, Inc). Sulfoxaflor was formulated as an EC025 (A17743A).

2.3 Membrane preparation

Crude membranes were prepared from mixed populations of *Myzus persicae* clone 4106A (originally obtained from Rothamsted Research) or FRC-P *Myzus persicae* (mixed ages). Aphids (approximately 5 g) were homogenised on ice in 16 mL of prechilled homogenisation buffer (0.05 M Tris base, pH 7.4, with HCl, 200 µM PMSF) with a motor-driven Ultra Turrax (5 × 20 s bursts, level 4.5). The homogenate was centrifuged (2000 × g, 30 min at 4 °C), and the resulting supernatant was filtered through two layers of prewetted mira cloth before a final centrifugation (83 000 × g, 60 min at 4 °C). The pellet (crude membrane) was resuspended in chilled, freshly prepared binding buffer (0.05 M Tris, 0.12 M NaCl, 100 µM EDTA, pH 7.4, HCl), beaded into liquid N_2 and stored at −80 °C. The protein concentration was determined by Bradford assay using BSA as a standard.

2.4 Saturation binding

[^{3}H]-Methyl-SFX (**32**, 2.81 TBq mmol^{-1}, purity >95%, in-house synthesis) and cold methyl-SFX (**16**, non-specific ligand) were prepared in buffer A (25 mM HEPES, 1 mM $CaCl_2$, pH 7.6, KOH). Crude aphid membranes were defrosted on ice and diluted to 3 mg mL^{-1} in buffer A. Incubations were carried out in glass tubes, with a final volume of 1 mL. The order of addition was buffer A, 10 µM cold methyl-SFX or control and [^{3}H]-methyl-SFX, at the indicated concentrations, followed by 350 µg of membranes. Reactions were equilibrated over a 70 min period at room temperature with constant shaking and stopped by placing the tubes on ice for 10 min, followed by filtration using a Brandel harvester. Filtration was onto Whatman G/F B filters presoaked in cold buffer A with 0.5% polyethylenimine. Filters were rapidly rinsed in a two-wash cycle (3 mL) with ice-cold buffer A, removed, allowed to air dry for 12 h and soaked (6 h) in 10 mL of scintillant (ScintSafe Gel; Fisher) prior to counting. [^{3}H]-IMD saturation isotherms were as described previously.[8]

2.5 Competition binding assays

Competition binding assays for [^{3}H]-methyl-SFX were performed in a final volume of 1 mL (buffer A) containing 350 µg of *M. persicae* membrane protein. [^{3}H]-methyl-SFX (to give 1 nM final concentration) and 5 µL of various concentrations of competing ligands in 5% DMSO were added. Controls contained 5% DMSO. Competing ligands were generally tested at seven concentrations in duplicate, spanning the range from 0.5 pM to 10 µM. Filtration and washing used a Brandel cell harvester. Competition binding assays for [^{3}H]-IMD were performed in microtitre plates in a final volume of 200 µL (buffer B) containing 100 µg of *M. persicae* membrane protein. [^{3}H]-IMD (to give 1 nM final concentration) and 20 µL of various concentrations of competing ligands in 1% DMSO were added. Controls also contained 1% DMSO. Competing ligands were generally tested at 12 concentrations in duplicate, spanning the range from 0.5 pM to 40 µM. Filtration and washing used a Tomtec cell harvester.

2.6 Aphicidal testing

Aphid populations used in this study were sourced and bioassayed as previously described.[23] Test pots (45 mm diameter) were prepared with discs of Chinese cabbage on tap water agar adapted from Herron *et al.*[24] A total of 20–30 mixed-age aphids were transferred to the dishes and allowed to settle for 24 h at 21 °C with a 16:8 h light regime. Dead individuals were removed prior to insecticide application. Serial dilutions of insecticide were applied using a Burkhard Potter precision laboratory spray tower.[25] Each treatment replicate was sprayed with 3 mL of solution at 0.6 bar, with a 3 s settling time (equivalent to approximately 400 L ha^{-1}). A minimum of five insecticide concentrations and three replicates per treatment were utilised in each test. At 72 h after application, individual aphids were scored and recorded as either dead (including seriously affected) or alive. LC_{50} values were calculated by LOGIT analysis using a Syngenta internal program (ACSAPwin).

2.7 Aphid electrophysiology

The effects of sulfoxaflor, imidacloprid and nitenpyram on spontaneous spike frequency in the aphid nerve cord were determined as follows according to the authors' original method (unpublished, but it will be described in detail elsewhere).[26] In brief, unstimulated multi-unit recording of spike activity was made using an extracellular suction electrode positioned just posterior to the exposed thoracic ganglionic mass of apterous adult *Tuberolachnus salignus*. Signals were filtered through a HumBug 50 Hz/60 Hz noise eliminator (Quest Scientific Corp.), captured to computer via an Axon Digidata 1322A interface (Molecular Devices Corp.) as a gap-free recording and analysed using the PClamp 10 data analysis program Clampfit (Molecular Devices Corp.) to produce histograms of spike frequency.

Test solutions were prepared by directly dissolving aliquots of a 10 mM acetone stock solution into experimental Ringer solution, followed by sonication to produce a final concentration of 1 µM. Test compounds were applied to the bath by connection to a continuous gravity-driven perfusion system set at a flow rate of 1 mL min^{-1}. Acetone at 100 ppm had no effect on spike frequency (data not shown).

2.8 Data analysis

The dissociation constant (K_d) and the maximal binding capacity (B_{max}) for methyl-sulfoxaflor and imidacloprid were determined by non-linear regression using models of one- and two-site curve-fitting functions of GraphPad Prism software (GraphPad Software, Inc., La Jolla, CA). Dose–response data were analysed by non-linear regression and expressed as the concentration producing half-maximal displacement (IC_{50}). Inhibition constant (K_i) values were calculated using the respective dissociation constants derived from methodological procedures adapted from those described for competition binding assays.

3 RESULTS

3.1 Saturation binding

To facilitate understanding on the mode of action of sulfoxaflor, a custom-synthesis tritiated sulfoxaflor analogue with high specific activity was prepared, [^{3}H]-methyl-SFX, as described in Section 2. Experimental conditions that allowed high-level, reproducible specific binding of [^{3}H]-methyl-SFX to *Myzus persicae* (clone 4106A) crude membranes were established. Analysis of the binding revealed a relatively low-abundance but high-affinity binding site (B_{max} = 78 fmol mg^{-1} protein, K_d = 2.7 nM) (Fig. 2a). Scatchard analysis of the data was monophasic, indicating the presence of only a single high-affinity binding site under the conditions examined. In contrast, as previously described,[8,27] the [^{3}H]-IMD binding fitted best to a two-site model: one site of high affinity with $K_d \sim 0.083$ nM and $B_{max} = 100 \pm 55$ fmol^{-1} mg, and a second binding site of lower affinity with $K_d \sim 1.7$ nM and $B_{max} = 298 \pm 48$ fmol mg^{-1} (Fig. 2b).

Reproducing previous findings, sulfoxaflor was relatively weak at displacing [^{3}H]-IMD in this study, with K_i = 32 nM[12] (Fig. 3). In contrast, however, sulfoxaflor displaced [^{3}H]-methyl-SFX with 100-fold greater potency, with K_i = 0.2 nM (Fig. 3). This confirms the validity of using methyl-SFX as a close surrogate for investigating sulfoxaflor invertebrate pharmacology.

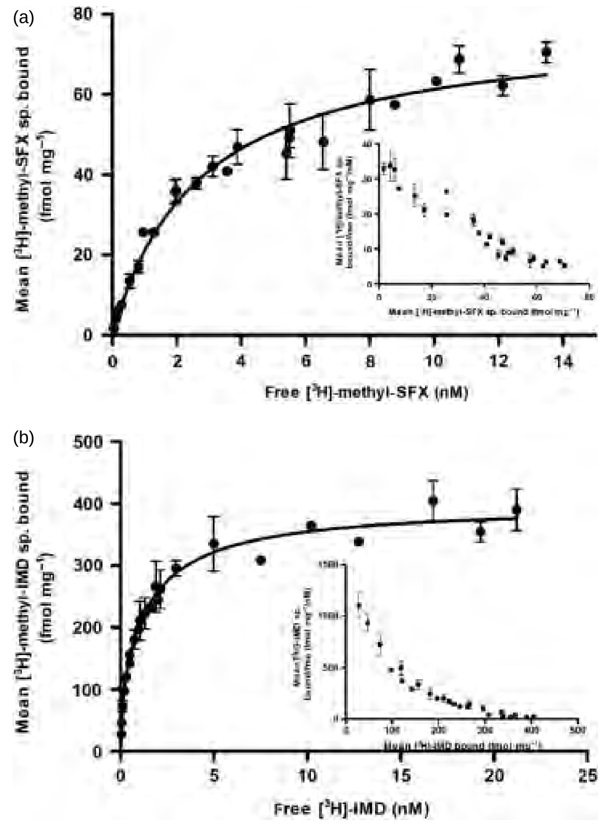

Figure 2. (a) Saturation isotherms of [^{3}H]-methyl-SFX and [^{3}H]-IMD binding to *Myzus persicae* membranes. Membranes were incubated with [^{3}H]-methyl-SFX (0.05–13.5 nM) for 70 min at room temperature. Non-specific binding was determined in the presence of 10 μM unlabelled methyl-SFX. Inset, Scatchard plot of [^{3}H]-methyl-SFX binding to *M. persicae* membranes. Data shown are the mean ± SEM from two separate experiments, each with duplicate determinations of total and non-specific binding. (b) Membranes were incubated with [^{3}H]-IMD (0.03–21 nM) for 90 min at room temperature. Non-specific binding was determined in the presence of 0.1 μM unlabelled MLA. Inset, Scatchard plot of [^{3}H]-IMD binding to *M. persicae* membranes. Data shown are the mean ± SEM from three separate experiments, each with duplicate determinations of total and non-specific binding (previously shown in Bass *et al.*[8]).

3.2 Biological relevance of binding

To demonstrate further the relevance of the high-affinity [^{3}H]-methyl-SFX binding site in crude *Myzus persicae* membranes, a selection of sulfoxaflor analogues were evaluated for displacement potencies and correlated with their aphicidal toxicity (Table 1). A clear correlation between toxicity and K_i displacement potency was observed (Fig. 4). The same sulfoxaflor analogues were investigated for displacement potency against [^{3}H]-IMD (Fig. 4). A correlation was also observed here; however, the sulfoxaflor analogues were all relatively weak at displacing [^{3}H]-IMD. Therefore, the dynamic range of IC_{50} values was much narrower, with the most potent compound only differing from compounds with no insecticidal activity by less than 100-fold.

3.3 nAChR pharmacology

Demonstrating the novelty of the binding site with respect to non-nAChR insecticides, a range of standards with distinct modes of action at high concentration (1 ppm) were only very weak at displacing [^{3}H]-methyl-SFX (Table 2). To address specifically whether [^{3}H]-methyl-SFX was interacting with nAChRs in *Myzus persicae* crude-membrane extracts, displacement studies were investigated using methyllycaconitine (MLA). Previous studies on insect MLA invertebrate pharmacology had demonstrated that it interacted only with nAChRs and importantly did not apparently distinguish between subtypes.[28] MLA potently displaced [^{3}H]-methyl-SFX with K_i = 0.37 nM (Fig. 5), very similar to the K_i observed in [^{3}H]-IMD competition experiments (Table 3).

To investigate the relationship between the sulfoxaflor binding site and neonicotinoids, similar displacement studies were carried out. Thiacloprid was exceptionally potent at displacing [^{3}H]-methyl-SFX, with K_i in the pM range (45 pM) (Fig. 5). Additionally, both IMD and clothianidin also displaced [^{3}H]-methyl-SFX, with K_i values in the pM range (Table 3). All three of these neonicotinoids are believed to share the same binding site, given their similar potency to displace [^{3}H]-IMD (Table 3). Neonicotinoids that are known to have a distinct binding site to IMD (most likely different nAChR subpopulations) were also investigated. Dinotefuran only displaces [^{3}H]-IMD in the very high nM range.[29–31] However, it was a relatively potent displacer of [^{3}H]-methyl-SFX, with a K_i value of 3.2 nM (Table 2). Additionally, both nicotine and TMX were more potent at displacing [^{3}H]-methyl-SFX than [^{3}H]-IMD (Table 2).

To further compare sulfoxaflor with neonicotinoids, the effects *in situ* on the exposed aphid nervous system were examined. Sulfoxaflor produced a rapid blockade of spontaneous neuronal activity, similar to the blockade produced by both nitenpyram and imidacloprid (Fig. 6).

3.4 Sulfoxaflor cross-resistance in FRC *M. persicae*

A clone of *Myzus persicae* (clone FRC-P) with high-level neonicotinoid resistance caused by a combination of upregulated metabolic capability and a single point mutation in the extracellular ligand-binding domain loop D region of the nAChR β1 subunit, resulting in an arginine to threonine substitution (R81T), has

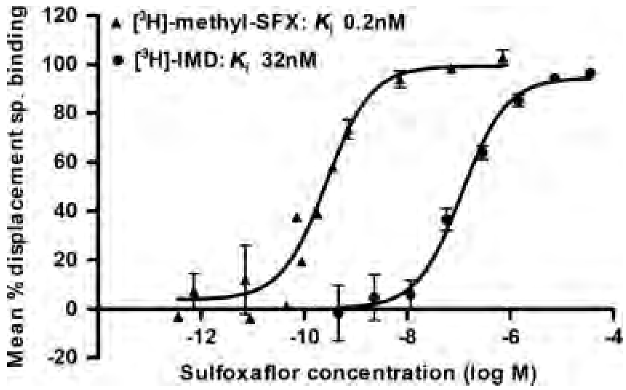

Figure 3. Differential potency of sulfoxaflor to displace [^{3}H]-methyl-SFX or [^{3}H]-IMD from *Myzus persicae* membranes. Membranes were incubated with SFX and either a fixed concentration of [^{3}H]-methyl-SFX (1 nM) at a final volume of 1 mL for 70 min at room temperature or [^{3}H]-IMD (1 nM) at a final volume of 200 µL for 90 min at room temperature. Data points represent the means of at least three independent experiments.

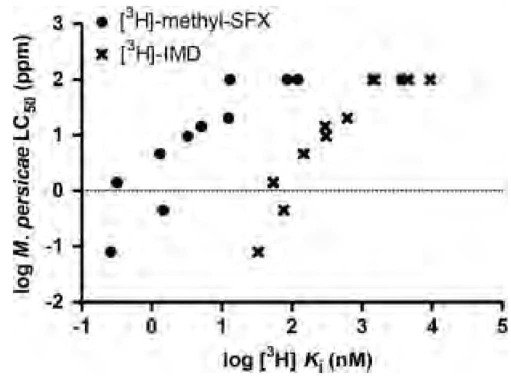

Figure 4. Sulfoxaflor analogue aphicidal contact toxicity better correlates with [^{3}H]-methyl-SFX displacement potency than with [^{3}H]-IMD displacement potency. Correlation between sulfoxaflor analogue insecticidal activity against *M. persicae* [LC_{50} (ppm)] and potency to displace [^{3}H]-methyl-SFX or [^{3}H]-IMD from membranes of *M. persicae*. For ease of visualisation, values of LC_{50} > 100 ppm (not possible to determine LC_{50} value accurately) are considered as 100 ppm.

Table 1. K_i values for sulfoxaflor analogues in [^{3}H]-methyl-SFX and [^{3}H]-IMD competition binding studies performed on *Myzus persicae* membranes

Compound number	[^{3}H]-Methyl SFX K_i (nM)	[^{3}H]-IMD K_i (nM)	*M. persicae* LC_{50} (ppm)
8	0.26	32.9	0.08
10	122	4571	>100
12	86	1514	>100
15	13	1428	>100
16	1.5	76.6	0.45
17	12	620	20.5
18	1.3	147	4.64
20	3600	9428	>100
28	3600	Not tested	>100
29	3.3	309	9.6
30	5.1	299	14.43
31	0.32	54	1.4

Table 2. A variety of distinct insecticidal modes of action at high concentration do not significantly displace [^{3}H]-methyl-SFX in *Myzus persicae* membranes (fixed concentration of test compounds at 1 ppm)

Compound	Mode of action	% Displacement of [^{3}H]-methyl-SFX
λ-Cyhalothrin	Na^+-channel modulator	3
Dinoseb	Mitochondrial uncoupler	13
Aldicarb	AChE inhibitor (carbamate)	0
Veratadine	Ca^{2+}-channel blocker	18
Pirimiphos methyl	AChE inhibitor (organophosphate)	2
Abamectin	Cl^--channel activator	−6
Chlorantraniliprole	Ryr receptor modulator	8
Fipronil	$GABA_A$ blocker	30

recently been described.[8] To investigate whether cross-resistance to sulfoxaflor was observed in the neonicotinoid-resistant aphid population FRC-P, spray application bioassays, which combine direct insecticide contact and subsequent exposure to residues on leaves, were performed. Measured resistance factors for the current commercialised neonicotinoids were observed, ranging between 54- and 3013-fold (Table 4). High-level resistance (43-fold) was also observed for sulfoxaflor, clearly demonstrating variable but high levels of resistance to all neonicotinoid insecticides.

The effects of the nAChR point mutation on sulfoxaflor pharmacology were investigated by preparing crude membranes from FRC-P. There was a complete absence of high-affinity [^{3}H]-methyl-SFX binding over the concentration range tested (Fig. 7).

4 DISCUSSION

Sulfoxaflor is a new insecticide from Dow Agrosciences with a nAChR-linked mode of action. However, the nature of the binding site and its relation to the existing neonicotinoids is currently unclear.[10,12,13] To facilitate a greater understanding of the mode of action of sulfoxaflor, a close analogue (methyl-SFX) was tritiated. Radioligand binding studies with [^{3}H]-methyl-SFX permitted the identification of a high-affinity site (K_d = 2.7 nM) present at relatively low concentrations (B_{max} = 78 fmol mg^{-1}) in *Myzus persicae* crude membranes, which importantly was potently displaced by sulfoxaflor (K_i = 0.2 nM). Validating the biological relevance of the binding site, a correlation was observed between aphicidal toxicity and [^{3}H]-methyl-SFX displacement potency for a range of sulfoxaflor analogues. The correlation of the same sulfoxaflor analogues with [^{3}H]-IMD displacement potency was poorer, with much less discrimination between biologically potent and inactive compounds. Additionally sulfoxaflor was over 100 times less potent at displacing [^{3}H]-IMD by comparison with [^{3}H]-methyl-SFX. Collectively, this clearly validates the use of [^{3}H]-methyl-SFX as a close surrogate to investigate the sulfoxaflor mode of action. The correlation data also imply that there is a linkage between the binding sites measured in the [^{3}H]-methyl-SFX and the [^{3}H]-IMD competition assays.

Binding assays are an unbiased approach for the identification of the relevant target protein through the characterisation of the highest-affinity interaction of the radioligand in extracts from the target organism. Therefore, having validated the biological relevance of the [^{3}H]-methyl-SFX binding site, the authors sought to explore sulfoxaflor pharmacology to allow an understanding of

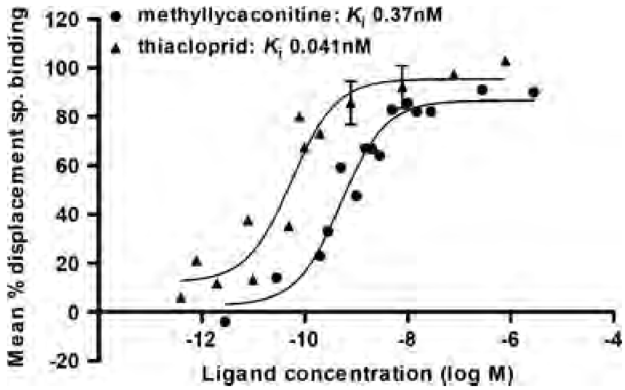

Figure 5. Potent displacement of [^{3}H]-methyl-SFX from *Myzus persicae* membranes by nicotinic ligands. Membranes were incubated with thiacloprid or methyllycaconitine (MLA) and a fixed concentration of [^{3}H]-methyl-SFX (1 nM) at a final volume of 1 mL for 70 min at room temperature. Data points from two independent experiments.

Table 3. Comparative neonicotinoid and nicotinoid evaluation in [^{3}H]-methyl-SFX and [^{3}H]-IMD competition binding studies performed on *Myzus persicae* membranes ($n = 2$)

Compound	Displacement of [^{3}H]-IMD [mean K_i (nM)]	Displacement of [^{3}H]-methyl-SFX [mean K_i (nM)]
Imidacloprid	0.55	0.035
Thiacloprid	0.17	0.041
Clothianidin	2.7	0.058
Nitenpyram	3.5	0.19
Sulfoxaflor	32	0.2
Methyl sulfoxaflor	85	1.5
Dinotefuran	336	3.2
Thiamethoxam	2900	481
Nicotine	800	146
Methyllycaconitine	0.15	0.37

its mode of action. A range of insecticidal standards with distinct modes of action at high concentration had little to no effect in [^{3}H]-methyl-SFX displacement experiments, ruling out any of these respective targets. As sulfoxaflor has been hypothesised to interact with the nAChR, displacement experiments were investigated with a range of nicotinic ligands. MLA is believed to interact with all nAChR populations in aphids and was a potent displacer of [^{3}H]-methyl-SFX with a sub-nM K_i.[28] However, the B_{max} for MLA (1290 fmol mg^{-1}) is far higher than for [^{3}H]-methyl-SFX (78 fmol mg^{-1}), demonstrating that sulfoxaflor can only be interacting with a subpopulation of the total nAChR pool.[28] Further linking in the nAChR as the target protein for sulfoxaflor, nicotine was more potent at displacing [^{3}H]-methyl-SFX than [^{3}H]-IMD.

These results are powerful evidence linking the biologically relevant, high-affinity sulfoxaflor binding site in *Myzus persicae* to the nAChR, the remaining question is to understand the relationship between sulfoxaflor and neonicotinoids. The nAChR pharmacology of the neonicotinoids is complex. Neonicotinoids that have nM potency to displace [^{3}H]-IMD, can be considered to share the same binding site, e.g. clothianidin and thiacloprid. However, thiamethoxam and dinotefuran are weak in [^{3}H]-IMD displacement studies and, based on respective radioligand binding studies, are believed to interact with distinct nAChR populations.[29,31–35] To add to this complexity, and reproducing previous findings, sulfoxaflor is relatively weak at displacing [^{3}H]-IMD.[10,12] Interestingly, however, IMD, clothianidin and thiacloprid all displaced [^{3}H]-methyl-SFX with pM K_i values, demonstrating a highly potent interaction for IMD-like neonicotinoids at the sulfoxaflor binding site. Dinotefuran, although more potent in displacement studies with [^{3}H]-methyl-SFX by comparison with [^{3}H]-IMD, was still approximately 100-fold weaker compared with the IMD-like neonicotinoids, suggestive of binding site differences. A similar observation was made for TMX, which was significantly more potent at displacing [^{3}H]-methyl-SFX than [^{3}H]-IMD, but with a K_i value too high for this nAChR binding site to be considered responsible for its insecticidal effects. The fact that TMX followed the trend of all the other neonicotinoids is further evidence that TMX has a *bona fide* nAChR binding site, as previously demonstrated.[33] IMD is known to have two distinct binding sites in hemipteran insects: a sub-nM-affinity but low-abundance site and a low-nM-affinity site at higher abundance.[8,27,36] The fact that the sulfoxaflor binding site is present at relatively low abundance (in a B_{max} range similar to that of the sub-nM site of IMD) and is displaced at pM concentrations by IMD is highly suggestive that sulfoxaflor is selectively interacting at the high-affinity IMD nAChR binding site. This would explain why sulfoxaflor is relatively weak in [^{3}H]-IMD displacement studies, where the tracer ligand is present at a concentration in which occupancy at both sites can be expected. The fact that sulfoxaflor can fully displace [^{3}H]-IMD at high concentrations does imply that it can weakly interact with the lower-affinity IMD site. However, it can be argued that this secondary site has lower biological relevance, given that potency to displace [^{3}H]-IMD by sulfoxaflor analogues has a weaker correlation with aphicidal toxicity in the susceptible strain 4106A. Estimating the affinity of sulfoxaflor at this lower-affinity site provides a K_i value of 32 nM. However, in studies with [^{3}H]-methyl-SFX, a second site of this lower affinity was not detectable owing to the difficult nature of working with the radioligand at high concentrations (above 20 nM). Indeed, it might be postulated that [^{3}H]-methyl-SFX is a better tool than [^{3}H]-IMD with which to correlate intrinsic neonicotinoid activity with insecticidal toxicity in sucking pests. In total, these *in vitro* receptor pharmacological studies point to the fact that sulfoxaflor has an IMD-like profile with potent biological activity driven by a single high-affinity binding site. To compare the effects of sulfoxaflor and neonicotinoids on the live insect nervous system, *in situ* measurements of neuronal activity from the exposed nerve bundle of *T. salignus* were performed. Imidacloprid (a nitroguanidine) and nitenpyram (a nitroenamine) both caused a rapid blockade of spontaneous action potentials, and an identical effect was also observed with sulfoxaflor. This observation is consistent with the behaviour of neonicotinoids on *Periplaneta americana* nerve preparations.[29,37] Although the aphid nervous system has been less characterised than that of *P. americana*, drawing on the analogy, and from sulfoxaflor studies on isolated *Carausius morosus* nerves, it can be hypothesised that the effects of sulfoxaflor in the aphid nervous system are due to a rapid desensitisation of nAChRS.[13] Therefore, at both the receptor and neuronal level, sulfoxaflor behaves in a manner akin to imidacloprid in aphids.

A number of different insect pests have developed commercially relevant resistance to neonicotinoids, and the prevalence is increasing. In almost all cases where the mechanisms of resistance have been identified, enhanced metabolism by monoxygenases plays some role. These include *Bemisia tabaci*,[9] *Leptinotarsa*

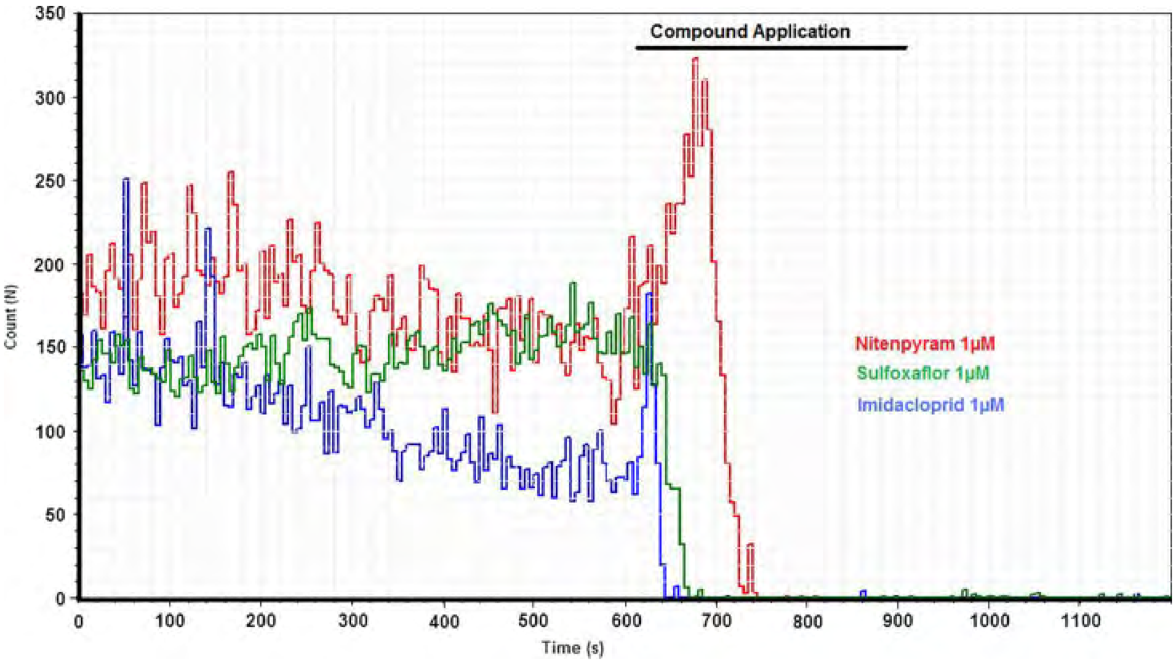

Figure 6. Sulfoxaflor, imidacloprid and nitenpyram all show a similar blockade of spontaneous neuronal activity in the aphid CNS. Representative traces are shown from extracellular recordings of the exposed nervous system of *Tuberolachnus salignus* before and after application of 1 µM IMD ($n = 15$), SFX ($n = 8$) or nitenpyram ($n = 2$) in the bathing solution.

Table 4. Neonicotinoid efficacy for the control of susceptible (4106A) and resistant (FRC) *Myzus persicae* strains

Insecticide	LC_{50} (ppm) (95% CL) 4106A	Slope ($\pm$ SE)	LC_{50} (ppm) (95% CL) FRC-P	Slope ($\pm$ SE)	RF_{50}
Thiamethoxam[a]	0.5 (0.4–0.6)	4.41($\pm$0.37)	108 (69.5–185)	2.94($\pm$0.51)	270
Imidacloprid[a]	0.1 (0.1–0.2)	7.82($\pm$1.37)	235 (142–476)	1.88($\pm$0.28)	2350
Sulfoxaflor	0.1 (0.1–0.2)	4.59($\pm$0.49)	4.3 (3.7–5.0)	5.16($\pm$0.49)	43
Clothianidin	0.3 (0.3–0.4)	6.76($\pm$0.89)	904 (478–3616)	1.71($\pm$0.38)	3013
Acetamiprid[b]	0.6 (0.5–0.6)	7.73($\pm$0.69)	49.3 (35.2–72.0)	4.65($\pm$0.87)	82
Thiacloprid[b]	0.4 (0.3–0.4)	5.10($\pm$0.39)	>1000	1.12($\pm$0.46)	>2500
Dinotefuran	10 (8.2–12.5)	5.21($\pm$0.69)	538 (434–696)	3.43($\pm$0.37)	54
Nitenpyram	1.3 (1–1.6)	5.38($\pm$0.75)	236 (93–3566)	1.93($\pm$0.48)	182

[a] Thiamethoxam and imidacloprid data previously presented in Bass *et al*.[8]
[b] Acetamiprid and thiacloprid data previously presented in Slater *et al*.[23]

decemlineata,[38] *Nilaparvata lugens*[39] and *Myzus persicae*.[8,40] One of the strengths of sulfoxaflor, compared with commercialised neonicotinoids, is the ability to withstand monoxygenase attack, and so sulfoxaflor effectively controls neonicotinoid-resistant *Bemisia tabaci* strains that have upregulated metabolic capabilities.[10] During the course of the present study there were similar findings for neonicotinoid-resistant whitefly (data not shown). A joint publication from Syngenta and Rothamsted Research recently described the first report of field-evolved target-site resistance to neonicotinoids in *Myzus persicae* (clone FRC-P).[8] Resistance in this aphid strain is conferred both through enhanced metabolic detoxification and a single point mutation of the nAChR β-subunit, an arginine to threonine at position 81 in loop D. Based on homology modelling and site-directed mutagenesis, the presence of this arginine, conserved in all insects sequenced to date, is believed to be critical for interaction with the electronegative pharmacophore, a common feature of all commercial neonicotinoids.[4,41,42] As sulfoxaflor is less susceptible to metabolic attack but retains an electron-withdrawing cyano group, an examination was carried out to determine whether clone FRC aphids displayed altered sensitivity to sulfoxaflor. Significant levels of resistance to sulfoxaflor, as well as all commercial neonicotinoids, were observed, at levels that have a major impact on the performance of these products under field conditions (unpublished data). It should be noted that all neonicotinoids generate lethality against FRC *Myzus persicae* when applied at sufficiently high concentrations in the laboratory environment. The effective lethal concentration of the neonicotinoid against FRC is most likely determined by a combination of interaction strength at the single remaining low-affinity IMD binding site and robustness to metabolic attack, as p450 enzymes are highly overexpressed in this aphid strain.

An interesting feature of FRC aphids is that they have completely lost the high-affinity [^{3}H]-IMD binding site, whilst the remaining lower-affinity site is present but altered in nature.[8] As evidence so far has pointed to the fact that sulfoxaflor interacts intimately with

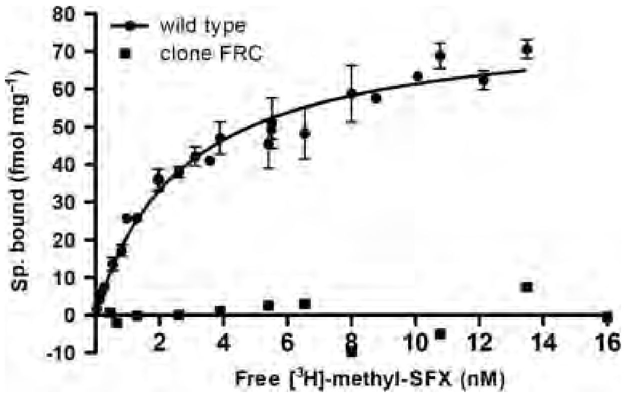

Figure 7. Absence of high-affinity [^{3}H]-methyl-SFX binding in membranes from the neonicotinoid-resistant FRC strain of *Myzus persicae*. Membranes were incubated with [^{3}H]-methyl-SFX (0.05–16 nM) in a final volume of 1 mL for 70 min at room temperature. Data shown are the mean ± SEM from two separate experiments, each with duplicate determinations of total and non-specific binding (W/T), or a single experiment (FRC).

the high-affinity [^{3}H]-IMD binding site, this aphid strain can be used to investigate the relationship between SFX and IMD, as it remains a remote possibility that the binding sites are distinct domains on nAChRs, linked by allosteric interactions. Interestingly, the [^{3}H]-methyl-SFX high-affinity binding site was completely absent in crude membranes from clone FRC (over the concentration range tested). Collectively, the results clearly demonstrate that the high-affinity SFX binding site and the IMD sub-nM-affinity site are identical. Therefore, sulfoxaflor is a nicotinic modulator sharing the same high-affinity binding site as imidacloprid. Based on the FRC *Myzus persicae* cross-resistance profile of all current commercialised neonicotinoids and sulfoxaflor, the authors suggest that sulfoxalfor should be added to the chemistry class termed neonicotinoids – the first member of the fourth generation possessing a novel *N*-cyanosulfoximine pharmacophore.

A recent study of nAChR subunits in the hemipteran *N. lugens* has suggested which subunits of the nAChR contribute to the formation of the imidacloprid binding site. This work has shown that the Nlβ1 subunit is an absolute requirement for imidacloprid binding, and that nAChRs containing Nlα1, Nlα2 and Nlβ1 constitute the lower-affinity site, whereas nAChRs containing Nlα3, Nlα8 and Nlβ1 constitute the higher-affinity site.[43] Whether a similar arrangement of nAChR subunits underlies the differential IMD affinity sites in aphids is not yet known.

The high-affinity IMD binding site is postulated to be only present in hemiptera, and has been suggested to underlie the exquisite sensitivity of this order to neonicotinoids.[27] The fact that the sulfoxaflor spectrum appears to be restricted to hemiptera further supports this hypothesis.[11] Neonicotinoids, such as imidacloprid, which interact at both the sub-nM- and low-nM-affinity sites, have a wider pest spectrum, as the low-nM-affinity site is present in a wide range of additional non-hemipteran insects. Sulfoxaflor may be expected to control non-hemipteran pests, but it requires much higher application rates as affinity at the low-nM IMD site is markedly weaker.[11]

5 CONCLUSION

Sulfoxaflor can be considered to be a neonicotinoid, the first member of the fourth-generation sulphoximine chemistry class, that acts at the high-affinity (sub-nM K_d) IMD binding site. This, in combination with its insensitivity to mono-oxygenase attack, in part explains its potent effects on hemipteran insects. Sulfoxaflor has been demonstrated by its manufacturers to have significant benefits over other selected neonicotinoids when used to control neonicotinoid-resistant insect pests, where their resistance is based on enhanced metabolism by monoxygenases. However, as demonstrated in this paper, there is significant risk that, where resistance is conferred by a modification at the target site of the neonicotinoid insecticides, the efficacy of sulfoxaflor could also be compromised. Although at the time of writing there is only evidence for one case of resistance based on an alteration at the target site, it is not unrealistic for more examples to be uncovered in the future, and it could even be speculated that the development of neonicotinoid insecticides that are designed to overcome metabolic resistance may increase selection pressure for target-site resistance modifications.

ACKNOWLEDGEMENTS

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BEYOND PESTICIDES
701 E Street, SE ▪ Washington DC 20003
202-543-5450 phone ▪ 202-543-4791 fax
info@beyondpesticides.org ▪ www.beyondpesticides.org

February 12, 2013

Office of Pesticide Programs (OPP)
Regulatory Public Docket (28221T),
Environmental Protection Agency,
1200 Pennsylvania Ave., NW.,
Washington, DC 20460-0001

Re: Proposed Conditional Registration of the New Insecticide Sulfoxaflor.
Docket Number: EPA-HQ-OPP-2010-0889

Dear Sir/Madam,

We are writing to urge the U.S. Environmental Protection Agency (EPA)* not to proceed with the proposed conditional registration of the new pesticide active ingredient, sulfoxaflor, its formulated technical product, and two end-use products for use in production agriculture. Sulfoxaflor is a new insecticide of the sulfoximine class and its proposed uses are for various vegetables, fruits, soybeans, wheat, and turfgrass, among other crops. The agency believes this decision to be in the public interest because "the registration of this pesticide for use on these crops will provide growers with a new pest management tool to kill a broad spectrum of piercing/sucking insects, including species that are difficult to control." However, there are many aspects of EPA's risk assessment for sulfoxaflor that we find troubling and which we believe should disqualify this chemical from being granted conditional registration.

Sulfoxaflor is highly toxic to honey bees according to EPA's ecological assessment, and there are still unanswered toxicological data gaps regarding honey bees, including field studies for assessing colony health and crop residues. Given the global phenomenon of bee decline and the recent precautions taken in the European Union regarding bee health with the suspension of certain neonicotinoid pesticides known to elicit adverse reactions in bees, it is irresponsible that the agency would allow yet another chemical with a high potential to be hazardous to bee health into the environment. It is also counterintuitive to current agency and interagency work to protect pollinators. We believe that the agency at this time should deny the registration of sulfoxaflor to avoid repeating past oversights and worsen current problems with bee decline.

Burgeoning Problems with the Conditional Registration Process

*See Appendix 1 Attached

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), 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.

Sulfoxaflor Poses Ecological Threats to Bee Populations

Neonicotinoids affect the nervous system of insects, causing irreversible blockage of the postsynaptic nicotinergic acetylcholine receptors (nAChRs) (via a selective agonistic mechanism).[1] 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.[2] Lethal and sublethal exposures have been shown to decrease foraging activity, along with olfactory learning performance and decreased hive activity.[3] 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

[1] USEPA. 2011. BEAD Chemical Profile for Registration Review: Clothianidin (044309). Federal Register Docket Id. No.: EPA–HQ–OPP–2011–0865
[2] Desneaux, N. et al., 2007. Sublethal Effects of Pesticides on Benefical Anthropods. Annual Review of Entomology, 52:81-106
[3] 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

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 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.

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.

Sulfoxaflor Not the Solution to Rising Neonicotinoid Resistance

While surveys have shown neonicotinoid resistance to still be restricted to very few species and often very localized in extent,[4] 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.[5] One study documented acetamiprid, clothianidin and thiamethoxam resistance at 6.4, 10, and 22-fold, respectively in cotton aphids (*Aphis gossypii).*[6] High levels of cross-resistance to thiamethoxam, imidacloprid, and acetamiprid have also been detected in silver whitefly (*B. tabaci*).[7] Insects with neonicotinoid resistance have also been shown to have varying resistance to organophosphates, carbamates, and pyrethroids.[8] 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[9]- 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.[10]

According to some industry scientists, sulfoxaflor has a pharmacological profile (in aphids) consistent with that of imidacloprid, suggesting that sulfoxaflor be considered a neonicotinoid.[11] However, others at Dow AgroSciences laboratories argue that the very high efficacy at nAChRs, coupled with its chemical structure, lack of cross-resistance, and metabolic stability,[12] 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

[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, 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
[6] 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.
[7] 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
[8] 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.
[9] 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
[10] 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
[11] Cutler P, Slater R, Edmunds AJ et al. 2012. Investigating the mode of action of sulfoxaflor: a fourth-generation neonicotinoid. *Pest Manag Sci.* doi: 10.1002/ps.3413.
[12] Watson GB, Loso MR, Babcock JM, et al. 2011. Novel nicotinic action of the sulfoximine insecticide sulfoxaflor. *Insect Biochem Mol Biol.* (7):432-9.

other neonicotinoid pesticides, making it a good candidate to control pests already resistant to certain neonicotinoids.[13,14] 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.[15]

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. Given that sulfoxaflor is more toxic than neonicotinoids, it is expected that it would be more toxic to honey bees, leading to disastrous consequences. We should not be introducing more potent insecticides into the environment as a solution to mitigating growing insect resistance. The solution to managing insect resistance is not to introduce more toxic chemicals, that would eventually give rise to more resistant strains, but to implement sound pest management techniques, including crop rotation, improving soil health, and shifting from a reliance on monocropping systems.

Section 18 Exemptions for Sulfoxaflor Already Put Bees at Risk

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.[16] 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 0.07ppm 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

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[13] 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.

[14] 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*

[15] 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)

[16] USEPA. 2012. Sulfoxaflor; Pesticides Tolerances for Emergency Exemptions. EPA-HQ-OPP-2012-0493; FRL-9361-4. Federal Register/Vol 77 No. 189.

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.

Human Health Assessment is Also Troubling

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.[17] While sulfoxaflor does have significant measurable neurotoxic 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.[18,19] 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

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17 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.

18 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

19 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.

an age that corresponds to early human adolescence. The authors conclude that these changes may have long-term adverse health effects in the offspring.[20]

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.

Impacts to Commercial Beekeepers Must be Considered

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.

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

[20] 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.

end, EPA must carefully consider the impact that registering sulfoxaflor would have on the livelihoods of commercial beekeepers.

Efficacy and Enforcement of Product Label

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.

Conclusion

Sulfoxaflor's pending registration is worrisome. The agency is aware of the problems related to honey bee populations in the U.S. and has even convened a Scientific Advisory Panel to discuss pollinator protection. EPA is also a part of other interagency activities investigating the bee decline phenomenon. Yet the agency finds it appropriate at this time to register a chemical that is "very highly toxic" to honey bees. This seems to be counterintuitive to the agency's work this past year. The agency believes that reducing the application rate and increasing application intervals is sufficient to protect these pollinators, but the many uncertainties and the lack of real-world data do not support a sulfoxaflor registration. Additionally, sulfoxaflor has been observed to induce developmental abnormalities in rodent species, as well as benign and malignant tumors. These risks cannot be underestimated. Honey bees and other pollinators are facing a crisis right now to which EPA is failing to adequately respond. Recent developments in Europe to protect essential pollinators from chemical assault are underway, while EPA continues to stagnate.

A conditional registration of sulfoxaflor is a violation of the terms set out in Section 3(c)(7)(A), in that registration will pose "unreasonable adverse effects on the environment." This is even more evident knowing sulfoxaflor's highly toxic nature and given that pollinator populations in the U.S. are already at crisis levels. We therefore urge the agency not to approve sulfoxaflor's registration.

Respectfully,

Nichelle Harriott
Beyond Pesticides

George Hansen
American Beekeeping Federation

Cynthia Palmer
American Bird Conservancy

Richard Andrews
Boulder Innovative Technologies, Inc.

Jeff Anderson
California Minnesota Honey Farms

Tom Theobold
Beekeeper

Appendix 1

The following individuals also support these comments:

Name		**State**
Marilyn	Waltasti	AZ
Lorayne	Robertson	AZ
Cynthia	Roseborough	CA
Jeannie	Mckenzie	CA
Nancy	Black	CA
Sharon	McCarthy	CA
Christina	Roe	CA
Patsy	Lowe	CA
Kleomichele	Leeds	CA
Gail	Camhi	CA
Judith	Smith	CA
Diaa	Bohn	CA
Julie	Ostoich	CA
Cindy	Zimmermann	CA
Laura	Collins	CA
Susan	Eschbach	CA
Don	O	CA
Karan	Zopatti	CA
Chris	Nigro	CO
Peter	Fenstermacher	CT
Anne	Halvey	CT
Beth	Boyer	CT
Edith	Coleman	DE
Douglas	Heise	FL
Lisa	Jacobson	FL
donna	curcio	FL
Andre	Stellingsma	FL
J	Beverly	IL
Jill	Murtagh	IL
Renee	Richards	KY
John	Whyman	LA
Lu	Haner	MA
Marina	Vrouvlianis	MA
Alan	Papscun	MA
David	Bibo	MD
Catherine	Lowry	MD

Margaret	Gallagher	MD
Theresa	Hage	MD
Natalie	Dandekar	MD
Sharon	Dolleman	ME
Anthony	Glaza	MI
Aldon	Maleckas	MI
Brenda	Jellies	MI
rick	weller	MI
Anne	Swanson	MI
Don	Booker	MS
Judith	Foran	NE
sylvia	dwyer	NH
elizabeth	nelson	NJ
Lydia	Morken	NY
Adrienne	Kahn	NY
Lori-Ann	Kohler	NY
Joan	Grishman	NY
d	oper	NY
Floss	Shahbegian	NY
José	Colón	NY
Thomas	Goodhart	NY
Andrea	Sreiber	NY
Neil	Miller	NY
Bob	Klein	NY
Kathleen	Morris	OH
Patricia	Norman	OH
Erik	Van Anglen	OK
Karuna	Gatton	OR
Olga	S	ot
Jan Marinus	Prins	ot
Antonello	Imborgia	ot
Christopher	Evans	ot
Beth	Allen	PA
Sue	Pashko	RI
Robert	Peel	TN
Linda	McDowell	TX
Chris	Reeves	TX
Nancy	Widman	TX
Jerry	Watson	VA
Judith	Bartley	VA

Theodore	Karch	VA
Marie	Luisa	VA
Arielle	Wildman	VA
Amy	Todisco	VT
liz	frey	WA
Kathleen	Beavin	WA
Maria	Kusel	WI
Adria	Cannon	WI
Pamela	Gallegos	WI
Nancy	Hayden	WI