CENTER FOR FOOD SAFETY

February 12, 2013

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

RE: Proposed Conditional Registration of Sulfoxaflor; filed online at: www.regulations.gov

Docket No. EPA-HQ-OPP-2010-0889

Dear Sir/Madam,

The undersigned groups, Center for Food Safety, Pesticide Action Network of North America, American Bird Conservancy, and Friends of the Earth, are pleased to submit the following comments on the above-referenced docket on EPA's proposal to conditionally register the new active ingredient sulfoxaflor under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Together our groups represent a broad range of stakeholders who are concerned about the potential impacts of sulfoxaflor's conditional registration to beekeepers, pollinators generally, and other non-target species.

Center for Food Safety (CFS) is a Washington, DC-based public interest non-profit membership organization that also has offices in San Francisco, CA and Portland, OR. Since its founding in 1997, CFS has sought to ameliorate the adverse impacts of industrial farming and food production systems on human health, animal welfare and the environment. CFS has over 200,000 members nationwide.

Pesticide Action Network of North America (PANNA) is an Oakland-based non-profit corporation that serves as an independent regional center of Pesticide Action Network International, a coalition of public interest organizations in more than 90 countries. For 30 years, PANNA has worked to replace the use of hazardous pesticides with ecologically sound and socially just alternatives across the United States and around the world. PANNA provides scientific expertise, public education and access to pesticide data and analysis, policy development and coalition support to more than 100 affiliated organizations in North America. PANNA has more than 80,000 members across the U.S.

American Bird Conservancy (ABC) is a 501(c)(3) not-for-profit membership organization whose mission is to conserve native birds and their habitats throughout the Americas. ABC acts by

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safeguarding the rarest species, conserving and restoring habitats, and reducing threats, while building capacity in the bird conservation movement.

Friends of the Earth (FoE) is a national non-profit environmental organization, founded in 1969. With offices in Washington, DC and Berkeley, CA and members in all 50 states, FoE defends the environment and champions a healthy and just world. FoE works to ensure food, consumer products and emerging technologies are safe for people and the environment; fights for clean energy that helps people and protects our climate; defends our oceans, forests, and the communities that depend on them; and advocates to replace economic policies that fuel environmental destruction and social injustice with fair and sustainable approaches. FoE-US is part of Friends of the Earth International, a global network representing more than two million activists in 76 different countries.

Summary

Sulfoxaflor is similar to the neonicotinoid insecticides that are already in use, as it also acts on the nicotinic acetylcholine receptor (nAChR) in insects. The similarities in mode of action and toxicity present comparable risks to those exhibited by the neonicotinoids, especially for pollinator health and the consequent effects on beekeepers. The EPA risk assessment (RA) for sulfoxaflor has a number of data gaps and oversights that should preclude registration of sulfoxaflor at this time. The lack of required data on pollinator safety to meet FIFRA mandates is further magnified by lack of proper product labeling, a broken incident reporting system and the lack of necessary resources or will to enforce appropriate applications of pesticides. Current labels are inadequate in terms of protecting pollinators; the only course of action that EPA can take to protect pollinators and other non-target species is to deny conditional registration of sulfoxaflor. Additionally, there are potential impacts to other species that require more research, with slight acute toxicity identified in birds and mammals. Given numerous data gaps and uncertainties, and the potential for unreasonable adverse effects, sulfoxaflor does not satisfy the FIFRA criteria for conditional registration. It is not in the public interest to proceed as the agency has proposed with the conditional registration of sulfoxaflor.

Overview of Sulfoxaflor

Sulfoxaflor (SFX) is proposed to be applied as a foliar spray via ground or aerial application on a wide range of crops. Aerially-applied pesticides pose distinct risks from non-target drift that can affect adjacent lands and beneficial organisms. In particular, sulfoxaflor presents problems for honey bees, which are already facing severe population declines and colony health issues, resulting in major economic and personal harm to beekeepers.

Sulfoxaflor is a systemic insecticide that provides 7 to 21 days of residual control and targets insect nAChRs and affects the liver in mammals. It is fairly stable to abiotic degradation, leading to its ability to persist in the absence of microbes.[1] Sulfoxaflor biodegrades quickly in aerobic soil

[1] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Docket ID: EPA-HQ-OPP-2010-0889-0022. Page 32.

conditions (half-life <1d), but is more persistent in anaerobic conditions (half-life 113-120d)[2]. In aquatic conditions, the aerobic biodegradation half-life is 37-88 days and the anaerobic half-life is 103-382 days.[3] This data shows that sulfoxaflor can persist and affect ecosystems long after its application in certain conditions.

While sulfoxaflor may biodegrade rapidly in aerobic conditions, its soil degradates are mobile and "expected to be highly persistent in aerobic soil/aquatic systems."[4,5] Sulfoxaflor and all of its degradates should be included in all of the risk assessment calculations. The major degradate (X11719474 [X-474]) has a different mode of action and is less toxic than sulfoxaflor, but is also systemic and could be absorbed from the soil by target crops, or successive crops in the same fields because of its long half-life.[6] This would be of greater concern and would need to be revisited if a soil-applied use was approved, but is still an issue with the proposed application methods. One of the minor degradates (X11519540 [X-540]) is more toxic than sulfoxaflor but it forms at low concentrations so was mostly excluded from the risk assessments. For aquatic organisms, the RA only evaluated sulfoxaflor and X-540. While EPA asserts that "available evidence indicates that the X-474 degradate does not share the same MOA as the parent and is much less toxic based on measures of effect relevant to ecological risk assessment," this dismissal still represents a significant release of a compound into the environment about which little is known.[7] EPA goes on to state that "X-474 is expected to dominate the exposure resulting from use of sulfoxaflor," suggesting that it is irresponsible to exclude X-474 from both the aquatic and terrestrial RA.[8] The current RA is inadequate to assess the potential risks from the stable X-474 in the aquatic environment. For terrestrial organisms, the RA evaluates parent sulfoxaflor only. Given the rapid biodegradation of sulfoxaflor, and its metabolism into degradates in plant tissue, this is inadequate to protect terrestrial species that may be exposed to residues. The combination of water solubility, persistence, and toxicity (especially to bees and other insect pollinators) is particularly concerning because compounds with these same characteristics have shown adverse effects to non-target species. Sulfoxaflor and its degradates' persistence in the environment is concerning because of the numerous detrimental impacts to non-target organisms that have not been fully assessed.

Chemical Categorization

Sulfoxaflor should be considered a subcategory of the neonicotinoid class of insecticides rather than the first member of the sulfoximine insecticide class based on its similarities in mode of action and its structure that mimics the neonicotinoid toxicophore. This classification should be taken into account for insecticide resistance management plans.[9] While the applicant, Dow AgroSciences, has asserted in published literature that sulfoxaflor is the first insecticide in the new sulfoximine class

[2] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 33.
[3] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 33.
[4] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.
[5] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 37.
[6] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 46.
[7] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 8.
[8] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.
[9] Cutler P, et al. 2012. Investigating the mode of action of sulfoxaflor: a fourth-generation neonicotinoid. *Pest Manag Sci*. doi: 10.1002/ps.3413.

of chemicals[10] (distinct from the neonicotinoids), other assessments of the compound suggest that it may instead be a new subclass of the neonicotinoids.[11] EPA refers to sulfoxaflor as "the only member of the sulfoxamine subclass of neonicotinoid insecticides" in the beginning of its RA, but later mentions that it is distinct from the neonicotinoids for insecticide resistance management.[12] EPA should resolve this confusion and clarify that sulfoxaflor is a subclass of neonicotinoids in light of the conflicting information from the applicant and the agency.

An investigation of sulfoxaflor's mode of action found that it interacts with the high-affinity imidacloprid binding site in the insect's nAChR.[13] Sulfoxaflor also behaves in a method similar to imidacloprid *in situ* in aphids at both the receptor and neuronal levels.[14] These characteristics could pose problems for cross-resistance with neonicotinoids, and should be factored into insecticide resistance management plans. Most of the currently-identified resistance to commercialized neonicotinoids is caused by enhanced monooxygenase metabolism.[15] Sulfoxaflor is stable to monooxygenases, so it can control pests that have developed metabolic resistance to the neonicotinoids.[16] However, resistance can also be conferred by a target site mutation that sulfoxaflor was susceptible to in trials, a type of resistance that is not discussed in the RA's discussion of cross-resistance.[17,18] The levels of resistance to sulfoxaflor identified in strains with target-site mutations could have a major impact on field performance of these products.[19] Sulfoxaflor's mode of action is not yet fully understood, and initial results show some cross-resistance with neonicotinoids, which should lead to their categorization as neonicotinoids to manage insecticide resistance. The concerns about potential cross-resistance with commercial neonicotinoids should be further explored, and are not addressed adequately in the evaluation of sulfoxaflor's proposed registration.

Impacts on Honey Bees and Other Pollinators

A major issue with the proposed conditional registration of sulfoxaflor is that the pollinator studies submitted were incomplete and inconclusive. The current commercial neonicotinoids have been shown to have severe adverse impacts on honey bees and other non-target insects, which furthers concerns about the use of sulfoxaflor. Over the past decade, honey bee colonies nationwide have suffered record annual losses of typically about 30% to upwards of 90% in worst case situations. Pesticides have recently been identified as a primary contributing factor in these alarming population losses. Introducing yet another systemic, highly toxic insecticide to bee populations will only exacerbate these problems, contribute to the loss of beekeeper livelihoods, damage the agricultural economy, and threaten the diversity of our nation's food supply. Synergistic effects of

[10] Babcock JM, et al. 2010. Biological characterization of sulfoxaflor, a novel insecticide. *Pest Manag Sci*. 67(3): 328-334.
[11] Cutler P, et al. 2012.
[12] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 8.
[13] Cutler P, et al. 2012.
[14] Cutler P, et al. 2012.
[15] Babcock JM, et al. 2010.
[16] Cutler P, et al. 2012.
[17] Cutler P, et al. 2012.
[18] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 14.
[19] Cutler P, et al. 2012.

sulfoxaflor and other stressors (additional pesticides, parasites, etc.) have also not been addressed. It is crucial to examine the realistic uses of sulfoxaflor and assess its impacts in light of the environmental stressors already faced by pollinator populations. Given the uncertainties and initial results that point to significant acute hazards, sulfoxaflor presents unreasonable adverse effects to bee species.

Studies on individual bees (Tier I) showed that sulfoxaflor is highly acutely toxic to honey bees, but further Tier II studies were incomplete or methodologically flawed. This lack of information about honey bee toxicity is an unacceptable data gap that should prevent the registration of sulfoxaflor. EPA notes several concerns with the reliability of the Tier 1 data, including:

- use of maximum residue reported in pollen and nectar to represent exposure to all bee castes and all crops
- lack of chronic toxicity data for adult and larval bees (and longer-term exposure to pupae)
- selection of the toxicity endpoint from the larval toxicity test
- accuracy of consumption rate estimates used for various bee castes
- variation in pesticide residues in pollen and nectar
- conservation of pesticide dose from plant tissue to the hive[20]

The formulated material was three times more toxic to adult bees than the technical material and the oral toxicity was even higher.[21] Measured residues of sulfoxaflor in pollen at field-application rates are three orders of magnitude (1,000-times) higher than that for imidacloprid (up to 7ppm SFX versus 5ppb for IMD), resulting in a high adult acute risk quotient that is unacceptable.[22,23] Presence in pollen and nectar ensures that developing bees will be orally exposed, yet no clear evaluation of this toxicity has been done to date. Larval toxicity was slightly lower than for adults, yet real impacts on honey bee individuals and colonies under field conditions remain unknown. The chronic toxicity endpoints for adult and larval bees are missing because of limitations in the study design that precluded the use of results beyond day seven.[24] This list of uncertainties and deficiencies associated with the Tier 1 studies should be cause enough to preclude EPA from approving sulfoxaflor, but there are additional problems with the submitted semi-field studies.

EPA does not have an approved field study protocol; thus the agency has no valid field studies on which to evaluate SXF toxicity to honey bee colonies. Of the semi-field studies that were submitted, five of the six were conducted with less between 3% and 67% of the proposed maximum label rate for the US.[25] Without trials conducted at field-realistic exposure levels, EPA has no data to

[20] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 91.
[21] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration: Appendix D, Supporting Information for Honey Bee Risk Assessment. Docket ID: EPA-HQ-OPP-2010-0889-0026.
[22] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 84.
[23] Chauzat MP, et al. 2011. An assessment of honeybee colony matrices, *Apis mellifera* (Hymenoptera: Apidae) to monitor pesticide presence in continental France. *Environ Toxicol Chem.* 30(1): 103-111.
[24] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 92.
[25] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 11.

determine how bees, both individuals and colonies, will be affected by sulfoxaflor use. Even at the low doses that were evaluated, significant adult mortality on the day of spray application was observed, so while it is certain that higher doses will produce greater mortality, the extent of this toxicity has never been evaluated. Thus, EPA has no data on the maximal field exposure rate impacts on honey bees or any other pollinator on which to base a conditional registration. Brood and long-term colony health studies were not included or were unacceptable methodologically, compounding the unknown potential long-term chronic effects of sulfoxaflor. The long term stability and persistence of the compound indicates that chronic effects on hive populations will occur. Without information on realistic exposures, the risks associated with field usage cannot be dismissed or deemed acceptable. The evidence from the pollinator studies points to unreasonable adverse effects to honey bees, which precludes EPA from approving the conditional registration.

There are several areas where EPA suggests potential mitigation efforts for certain crops to reduce pollinator exposure (e.g., timing applications for late in the day for cucurbits), but these are only offered as voluntary applicator practices, not requirements. On the proposed label, application is required to avoid bloom periods for certain crops, but this is not adequate to protect pollinators from pre-bloom applications because of the systemic nature of sulfoxaflor. These mitigation efforts also do not reduce the likelihood of bees contacting sulfoxaflor via drift on to neighboring lands, and essentially ignore the higher exposure likelihood on the day of application. The systemic nature of sulfoxaflor and its major degradates means that these suggested mitigation measures will not be adequate to protect honey bees and other pollinators from exposures.

The risk assessment also fails to take into account the impacts on the livelihoods of beekeepers, the national agricultural economy, and localized rural economies. Honey bees are the most economically valuable pollinator worldwide, and many high-value crops such as almonds and broccoli are entirely reliant upon pollination services by commercial beekeepers. Of the 100 crops that provide 90 percent of the world's food, over 70 are pollinated by bees. The value of crops pollinated by bees in the U.S. alone was estimated at $19.2 billion in 2010 – that figure has since grown.[26] This clearly multiplies the economic impacts of past EPA decisions on conditional registrations that have taken a major toll on beekeeper livelihoods, and counsels strongly against any more conditional registrations for additional neonicotinoids such as sulfoxaflor.

- *Non-Apis bees and other beneficial insects*

The risk assessment's cursory treatment of the risks of sulfoxaflor to the ~4,000 species of native North American bees is unconvincing, a major failure given the severe declines many of these critical species are facing.[27] These bees lack the carefully-bred adaptability and resilient social structures of *Apis mellifera* and many have entirely different life cycles and vulnerabilities. Native species are at a far higher risk from pesticide toxicity than managed colonies of *A. mellifera*. The RA only mentions *Bombus* species in passing, and does not address other native pollinators. Acute oral

[26] Calderone NW. 2012. Insect Pollinated Crops, Insect Pollinators and US Agriculture: Trend Analysis of Aggregate Data for the Period 1992–2009. *PLoS ONE* 7(5): e37235.
[27] See, for example, Evans E, et al. 2009. Status Review of Three Formerly Common Species of Bumble Bee in the Subgenus *Bombus*, Xerces Society. Available at: www.xerces.org/wp-content/uploads/2009/03/xerces_2008_bombus_status_review.pdf .

toxicity to bumblebees is high, although the acute contact toxicity is lower than for honey bees. The oral toxicity of the formulated product is much higher for bumblebees than for honey bees, and toxicity for important native bee species is entirely unknown at this point. These unidentified additional effects on beneficial insect species should further dissuade EPA from registering sulfoxaflor prior to conducting comprehensive pollinator risk assessments.

There are numerous other beneficial insects and other invertebrates that are severely impacted by prophylactic applications of various commercial insecticides. EPA's knowledge of the impacts on these species is far more limited than its knowledge of the impacts on honey bees. Massive data gaps exist for beneficial non-bee insects such as butterflies, ladybugs and lacewings, dragonflies, hoverflies, and others, which are not addressed by the RA.

This section of the sulfoxaflor RA needs dramatic bolstering. If EPA proceeds with the current RA framework it appears likely that beneficial native insects, including rare and endangered species, will face continuing jeopardy. Given that many of these native species have small, localized native ranges, the assessment process should consider the need to restrict or limit the use of sufloxaflor in those locations, a consideration lacking in the document. Otherwise, exposure routes such as foliar spraying could effectively eliminate large portions of remaining populations of native bees and other beneficial insects. Overall, the applicant data submitted to EPA on *Apis* and non-*Apis* bees and other beneficial invertebrates is inadequate and fails to constitute an adequate effects analysis for Federally-listed threatened and endangered species as required by Section 7(a)(2) of the Endangered Species Act. This violates that Act and must be remedied.

Impacts to Aquatic Ecosystems

Aquatic ecosystems and the species that depend on them also face risks from systemic pesticides including sulfoxaflor. Surface water contamination resulting from the use of sulfoxaflor is expected to occur mainly from drift, rather than run-off. Plant residues that are left after crops are harvested are another potential route for surface water contamination. Drifted sulfoxaflor that reaches aquatic systems will likely persist, while that reaching soil systems is expected to break down quickly.[28] However, this assumption does not account for the major soil degradate, X-474, which is mobile and can run-off following sulfoxaflor application into surface waters. EPA states that "both surface and ground water contamination is expected from these three degradates following leaching drift/run-off events," clearly identifying a potential route of exposure for aquatic systems.[29] The RA does not assess the impact of the major degradate X-474 on aquatic environments, which should be remedied before sulfoxaflor is considered for registration.

While the acute toxicity to most aquatic species (flora and fauna) was determined to be fairly low, sulfoxaflor is highly acutely toxic to saltwater invertebrates.[30] This poses concerns for coastal uses of sulfoxaflor, but there is no apparent proposed mitigation through labeling or otherwise. Without mitigation and further exploration of sulfoxaflor's, and its degradates', toxicity to saltwater

[28] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.
[29] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.
[30] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 10.

invertebrates, the use of sulfoxaflor in coastal areas presents a serious threat to estuarine and marine ecosystems.

Chronic toxicity of sulfoxaflor to aquatic species is examined, but the possibility for contamination of surface waters above the levels of concern is not addressed. In a key recent paper, Starner and Goh (2012) document that a significant portion of sampled surface waters were contaminated with imidacloprid above EPA-allowed levels for chronic invertebrate exposure across diverse agricultural landscapes in California.[31] Several other studies by the U.S. Geological Survey have found comparable aquatic contamination from the systemic neonicotinoids, which are similar in action to sulfoxaflor, in other environmental contexts.[32] The aquatic persistence of sulfoxaflor and its degradates, especially in anaerobic conditions, suggests that there may be similar levels of sulfoxaflor detected in waterways should it be registered. However, the proposed RA framework does not mention these water contamination studies nor does it quantify the risks to other species from comparable sulfoxaflor water contamination. The fact this environmental contamination by a major neonicotinoid exists now in California and elsewhere is indicative of agency failure to prevent undue consequences in its past risk assessments. The sulfoxaflor RA must be revised to correct this omission, or similar water contamination from sulfoxaflor is likely to impact aquatic ecosystems.

Avian Toxicity

The environmental persistence of the sulfoxaflor degradates and their neonicotinoid-like mode of action raise health and environmental concerns that go well beyond invertebrates. EPA identifies slight acute toxicity risks to birds, but states that sulfoxaflor is "practically nontoxic" on a sub-acute dietary basis. However, the passerine study on zebra finches was incomplete, and the acute oral LD_{50} could not be determined.[33] This is an area of uncertainty in the avian acute risk estimation that should be addressed with a second study.[34] Data is also lacking on effects from consumption of contaminated drinking water for all species, and EPA says that "sulfoxaflor exposure through drinking water alone has the potential to be a relevant acute or chronic exposure route of concern for mammals or birds."[35] EPA also says that "additional refinements are needed to determine if actual risks result from this [drinking water] exposure pathway," but these refinements were not conducted.[36] This clearly shows a route of exposure and area of concern that is not adequately assessed by the EPA's RA that poses significant detrimental impacts to non-target species. In the case of imidacloprid, numerous recent studies have indicated surface water contamination exceeding EPA–recognized safe levels. The persistence of sulfoxaflor's metabolites in aquatic

[31] Starner K and Goh KS. 2012. Detections of the Neonicotinoid Insecticide Imidacloprid in Surface Waters of Three Agricultural Regions in California, USA, 2010-2011. *Bull Environ Contam Toxicol.* 88(3):316-21.
[32]Hladik ML and Calhoun DL. 2012. Analysis of the Herbicide Diuron, Three Diuron Degradates, and Six Neonicotinoid Insecticides in Water – Method Details and Application to Two Georgia Streams. USGS Scientific Investigations Report 2012-5206.; Smith KP. 2011. Surface-Water, Water-Quality, and Meteorological Data for the Cambridge, Massachusetts, Drinking-Water Source Area, Water Years 2007-08. USGS Open-File Report 2011-1077.
[33] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 68.
[34] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 90.
[35] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 109.
[36] EPA. Environmental Fate and Ecological Risk Assessment for Sulfoxaflor Registration. Page 20.

environments raises concerns similar to those posed by imidacloprid and other neonicotinoids. There are a number of concerns about the effects of neonicotinoids on avian species and the aquatic systems on which they depend that are only now being explored, and sulfoxaflor may pose similar threats.[37] Sulfoxaflor should not be approved without complete acute, subacute, and reproductive toxicity information on avian species, including completion of the passerine study.

Mammalian and Human Toxicity

Sulfoxaflor's potential mammalian and human toxicity has not been adequately evaluated. In carcinogenicity studies, increased incidence of interstitial cell tumors were observed but EPA does not consider these to be treatment related due to a lack of dose-response. Tremors, convulsions, hind limb splaying, etc. were also observed, and EPA is unsure about the cause of these. Significant hepatocellular adenomas were observed at high doses of sulfoxaflor in rats. Carcinomas and hepatocellular adenomas were seen in mice. Perputial gland tumors, while observed, were difficult to relate to treatment, leading to the agency's classification of sulfoxaflor as having "suggestive evidence of carcinogenic potential." Developmental abnormalities (skeletal, neonatal death) were observed in rats, liver weight and enzyme changes, hypertrophy, tumors were also observed in sub-chronic and chronic studies.

Despite these demonstrated effects, EPA believes that data are sufficient to support reducing the interspecies uncertainty factor to 3X for the developmental effects, even though many of the studies were lacking. One industry study observed that sulfoxaflor affected the fetal, not adult, rat muscle nAChR and that prolonged exposure causes sustained striated muscle contracture resulting in concomitant reduction in muscle responsiveness to physiological nerve stimulation. According to the study, fetal effects were inducible with as little as one day of exposure at the end of gestation, but were rapidly reversible after birth.[38] While sulfoxaflor does have significant measurable neurotoxic activity in mammalian systems (mice and rats), it has been concluded that these effects are not relevant to humans. A search of the literature found no other studies evaluating the effect of sulfoxaflor on mammalian systems and so, much is still unknown about this chemical's potency in humans.

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.[39,40] One study conducted at Duke University Medical Center found that gestational exposure to a single, nonlethal dose of imidacloprid produces significant neurobehavioral deficits and an increased expression of pathological alterations in several brain

[37] See forthcoming report from the American Bird Conservancy and toxicologist Pierre Mineau for more details.
[38] 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.
[39] 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.
[40] 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.

regions of the offspring of Sprague-Dawley rats, at an age that corresponds to early human adolescence. The authors conclude that these changes may have long-term adverse health effects in the offspring.[41] Results such as these should prompt a closer review of sulfoxaflor's potential impacts to mammals.

Even though there are no residential uses at this time, the Food Quality Protection Act (FQPA) safety factor should not be reduced from 10X to 1X, nor should the interspecies uncertainty factor be reduced to 3X since much is still unknown about developmental neurotoxicity susceptibility. Given the mode of action similarities between sulfoxaflor and neonicotinoids, the higher potency of sulfoxaflor, and its carcinogenic potential, an FQPA safety factor of 10X should be retained. Much is still unknown about sulfoxaflor's mammalian toxicity, so EPA should evaluate sulfoxaflor with conservative safety factors.

Conclusion

There are still many unanswered questions, especially with respect to pollinator health, that should preclude any form of registration of sulfoxaflor by EPA at this point. The available information points to potentially significant unreasonable adverse effects as well as major areas of critical impact uncertainty. Therefore, sulfoxaflor plainly does not satisfy the FIFRA criteria for conditional registrations and should not be registered.

If you have questions about this comment, please contact: Peter T. Jenkins, Attorney/Consultant, Center for Food Safety, 660 Pennsylvania Ave, SE, #302, Washington DC 20003. tel: 202.547.9359; email: pjenkins@centerforfoodsafety.org.

Sincerely,

Center for Food Safety

Pesticide Action Network

American Bird Conservancy

Friends of the Earth

[41] 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.