



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

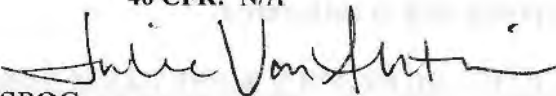
OFFICE OF CHEMICAL SAFETY AND  
POLLUTION PREVENTION


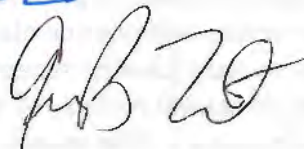
**MEMORANDUM**

September 14, 2012  
TXR #: 0056310

**SUBJECT:** **Sulfoxaflor:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of April 26, 2012: Recommendation on the need for a 28-day inhalation study.

<b>PC Code:</b> 005210	<b>DP Barcode:</b> N/A
<b>Decision No.:</b> N/A	<b>Registration No.:</b> N/A
<b>Petition No.:</b> N/A	<b>Regulatory Action:</b> N/A
<b>Risk Assessment Type:</b> N/A	<b>Case No.:</b> NA
<b>TXR No.:</b> 0056310	<b>CAS No.:</b> N/A
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Health Effects Division (HED; 7509P)

**THROUGH:** Jess Rowland, Co-Chair   
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HASPOC  
HED (7509P) 

**TO:** Michael A. Doherty, Ph.D., Chemist  
Edward Scollon, Ph.D., Toxicologist  
Zaida Figueroa, Industrial Hygienist  
Christina Swartz, Chief  
Risk Assessment Branch II (RABII)  
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And

Jennifer Urbanski and Venus Eagle  
Registration Division (RD; 7505P)

## MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jess Rowland, Jessica Ryman, Jonathan Chen, Michael Metzger, P.V. Shah, Ray Kent

Presenters: Michael Doherty, Ed Scollon, Christina Swartz

Other Attendees: Elizabeth Holman, Zaida Figueroa, Kristin Rury, Julie Van Alstine

## I. PURPOSE OF MEETING:

Risk Assessment Branch II (RAB II) is preparing a risk assessment for sulfoxaflor for use on numerous crops. Sulfoxaflor is new active ingredient and the first member of the sulfoximine class of insecticides. Sulfoxaflor is proposed for foliar application using ground- or aerial-based broadcast spray equipment. As a result of the registered use patterns, short- and intermediate-term exposures to aerosolized sulfoxaflor may occur.

The toxicity database for sulfoxaflor is largely complete, missing only the repeated exposure inhalation study. In the absence of that study, an oral study will be used to assess risks via the inhalation route of exposure. At the request of the RAB II team, the Hazard Science Policy Council (HASPOC) evaluated the need for a 28-day inhalation study in rats (26 April 2012) to support the proposed uses of sulfoxaflor.

## II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENTS:

Sulfoxaflor is a selective insecticide intended for use against various sucking/chewing insect pests that feed upon fruit and vegetable crops, turf grass (sod farm), and ornamental plants. It is the first member of the sulfoximine class of insecticides. Sulfoxaflor is an efficacious agonist of the insect nicotinic acetylcholine receptor, eventually resulting in paralysis and death. Furthermore, the structural novelty of sulfoxaflor makes it stable in the presence of monooxygenase enzymes. The monooxygenase enzymes are responsible for virtually all known cases of field pest resistance to the neonicotinoid class of insecticides, which also act via the nicotinic acetylcholine receptor.

The proposed formulations include a suspension concentrate (SC) and a water-dispersible granule (WDG). There are no proposed residential uses at this time. Occupational exposure is expected to be of short- to intermediate-term durations. The proposed personal protective equipment (PPE) for agricultural uses consists of long-sleeved shirt and long pants, shoes plus socks, and protective eyewear.

In the absence of a route-specific inhalation toxicity study, inhalation risks will be assessed based on decreased neonatal survival observed in the developmental neurotoxicity study (LOAEL = 7.1 mg/kg/day, NOAEL = 1.8 mg/kg/day). A 30-fold uncertainty factor including 3X for inter-species extrapolation and a 10x factor for intra-species variability will be used; therefore, the level of concern (LOC) is 30. Several mechanistic and guideline studies indicate the neurotoxicity is mediated through the fetal-type acetylcholinesterase nicotinic receptor.

These studies further indicate that humans are not expected to be more sensitive to sulfoxaflor toxicity via this route. Therefore the typical 10X factor for interspecies extrapolation is reduced to 3X (see below).

The estimated inhalation MOEs from occupational activities range from 130 for mixing and loading dry flowable formulations with baseline personal protective equipment (PPE) for aerial applications on cotton to 1,800,000 for mixing, loading, and applying with baseline PPE for backpack applications on turfgrass, with most of the values being greater than 1,000.

### III. STUDY WAIVER REQUESTS

#### **Inhalation Study**

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more protective. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical-chemical properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. Sulfoxaflor (MW = 277.3 g/mol) has a low vapor pressure ( $\leq 1.4 \times 10^{-6}$  Pa at 20°C;  $1.05 \times 10^{-8}$  mm Hg at 25°C) and an estimated Henry's Law Constant of  $5.8 \times 10^{-7}$  Pa m<sup>3</sup>/mol (unbuffered, 20°C; =  $4.4 \times 10^{-9}$  mm Hg m<sup>3</sup>/mol =  $5.7 \times 10^{-12}$  atm m<sup>3</sup>/mol). However, low vapor pressure and/or Henry's law constant does not preclude exposure to aerosolized droplets or particles/dusts.
2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation of droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. Sulfoxaflor is proposed for application using aerial and airblast equipment, which are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may also contribute to spray drift. In the case of sulfoxaflor, with the use of an oral POD, the highest inhalation exposure estimates (MOE = 130) are associated with mixer/loader activities for aerial application to cotton.



3. **Margins of Exposure (MOEs):** The MOE estimates for inhalation scenarios were calculated using the NOAEL from an oral toxicity study, and should be considered in the WOE analysis for an inhalation toxicology study waiver. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests (i.e., in the case of sulfoxaflor, higher than 300). The 2009 analysis suggests this approach is appropriate for most pesticides, but not all. Under the interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors discussed here. All worker exposures are assessed as short-and intermediate-term based on label-prescribed uses and expected exposure durations. In the case of sulfoxaflor, the MOE for occupational handlers that does not meet the waiver criterion for MOEs ranging from 10-100 times the LOC; the mixer/loader MOE for aerial application to cotton (130) is approximately 4 times the LOC of 30.
4. **Toxicity:** Sulfoxaflor and its metabolites have relatively low (Category III or IV) acute toxicity via oral, inhalation, and dermal routes of exposure in the rat and there is no evidence of dermal sensitization, minimum dermal irritation, and only slight eye irritation.

With the exception of a subchronic inhalation toxicity study, the toxicology database for sulfoxaflor is complete for risk assessment purposes, including the potential for increased susceptibility of infants and children.

When given to rats via the oral route, sulfoxaflor is rapidly absorbed; absorption estimates ranged between 92% and 96% with maximum plasma concentrations reached within 2 hours. As it is absorbed from the GI tract, sulfoxaflor is homogeneously distributed throughout the body without any tissues acting as major depots. Sulfoxaflor is rapidly eliminated from the body; 90% is excreted in the urine with the remaining portion excreted in the feces. Less than 10% of the recovered residue is as metabolites, and therefore, sulfoxaflor is not very amenable to *in vitro* metabolism.

Toxicity and mechanistic studies in rats, rabbits, dogs, and mice highlight the liver and the nervous systems as target organ systems. Liver effects in subchronic and chronic studies include organ weight and enzyme changes, hypertrophy, proliferation, and tumors. Long-term studies resulted in hepatic effects at lower doses than in the short-term studies. Neurological effects in the rat are manifested as limb flexure, bent clavicle, and convoluted/hydrourer in fetuses and decreased neonatal survival. These effects were not observed in the rabbit. As previously mentioned, several mechanistic and guideline studies indicate the neurotoxicity is mediated through the fetal-type acetylcholinesterase nicotinic receptor (nAChR). The fetal nAChR occurs in the skeletal muscle of neonate rats and is gradually replaced with the adult type receptor within a few weeks after birth. The fetal nAChRs are susceptible to agonism by sulfoxaflor, resulting in contraction of the skeletal muscles. These contractions result in curvature of the soft bones of the clavicle, a hunched appearance of the neonates, and constriction of the diaphragm muscles. The constriction of the diaphragm prevents proper breathing in

newborn offspring and they expire within 1 to 2 days of birth. The adult type nAChR in the rat is not responsive to sulfoxaflor nor is the fetal and adult type in the rabbit and human. Therefore, the rat appears to be uniquely sensitive to this avenue of neurotoxicity.

Sulfoxaflor is classified as having “suggestive evidence of carcinogenicity” based on a weight of evidence consideration of all observed tumors in rats. HED has concluded that the quantification of risk using a non-linear approach will adequately account for all chronic toxicity, including carcinogenicity that could result from exposure to sulfoxaflor. None of the data for the parent compound or its metabolites show any evidence of genotoxicity or mutagenicity.

Although there is clear evidence that there are neurological effects following exposure to sulfoxaflor, the level of concern for neurotoxicity is low because the effects are well characterized, they occur at excessive doses, and clear NOAELs are established. Although there is increased quantitative susceptibility in the developmental neurotoxicity (DNT) study, the level of concern for the increased susceptibility is low because the effects are well characterized, the mode of action is understood (M. Doherty, D382604), and the endpoints chosen for risk assessment are protective of potential *in utero* developmental effects. Therefore, HED is recommending that the required 10X FQPA Safety Factor be reduced to 1X.

HED further recommends that the 10X interspecies factor ( $UF_A$ ) be reduced to 3X for assessments based on nicotinic-receptor-mediated effects (i.e., acute dietary risk assessment for women of reproductive age and for dermal and inhalation risk assessments). This recommendation is based on the evidence gathered from extensive mechanistic data which address the mode of action in rats, and which also indicate that rats may be uniquely sensitive to the developmental effects of sulfoxaflor. In fact, humans may not be susceptible to these effects based on the lack of responsiveness of the human nicotinic receptor to sulfoxaflor in the agonism study. Furthermore, the observation that no neonatal deaths or neuromuscular/skeletal effects were noted in the rabbit developmental toxicity study supports the conclusion that rats are uniquely sensitive to developmental toxicity due to sulfoxaflor exposure. In addition, there is support for the pharmacodynamic differences in how sulfoxaflor interacts with rat and human receptors, as well as differences between fetal and adult receptors. These differences suggest that to the extent that neonatal death in rats occurs as a result of sulfoxaflor binding to the fetal receptor, these effects would not be observed in humans. Overall, these data suggest as a conservative assumption that rats and humans are at most pharmacodynamically comparable. The remaining component of the  $UF_A$  to address potential pharmacokinetic differences remains at 3X. Consequently, HED recommends that the interspecies UF be reduced to 3X for assessments based on nicotinic-receptor-mediated effects.

#### IV. HASPOC RECOMMENDATIONS:

**The HASPOC concludes, based on a weight of evidence (WOE) approach, that a 28-day inhalation toxicity study is not required for sulfoxaflor at this time.** The HASPOC considered all of the available hazard and exposure information for sulfoxaflor. Although the use of an oral POD results in an MOE of 130 that is only four-fold higher (i.e, not the acceptable 10-fold) than the than the Level of Concern (30), a repeated inhalation study is not expected to yield a lower POD because: 1) of the low vapor pressure (less hazardous); 2) the low acute inhalation toxicity (Toxicity Category IV); 3) the oral absorption is high (>90%) and rapid and thus substantially higher absorption *via* the inhalation route is not expected; 4) sulfoxaflor is not subject to enterohepatic circulation, making the absorbed oral dose available systemically; 5) sulfoxaflor is not subject to *in vivo* metabolism and therefore potential first-pass effects are not relevant; and 6) the mode of action and window of susceptibility are well understood for sulfoxaflor.

#### **References:**

Sulfoxaflor – New Active Ingredient Human Health Risk Assessment of Uses on Numerous Crops, M. Doherty, Draft, D382604.