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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

May 31, 2012
TXR # 0056324

SUBJECT: **Flumioxazin:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of April 26, 2012: Recommendations on a waiver request for a subchronic inhalation study.

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AND
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MEETING ATTENDEES:

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

Presenters: Deborah Smegal, Monica Hawkins

Other Attendees: Kristin Rury, Julie Van Alstine

I. PURPOSE OF MEETING:

The Hazard Science Policy Council (HASPOC) met on April 26, 2012 to discuss Valent USA Corporation's request to waive the requirement for a 28-day inhalation toxicity study for flumioxazin. Flumioxazin is an *N*-phenylphtalimide herbicide proposed for use on wheat, sunflower, safflower, flax, lentils, and field peas. Due to the potential for repeated inhalation exposure to flumioxazin, a 21/28-day rat inhalation study to support the registered and proposed uses of flumioxazin may be required.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:

Flumioxazin, 2-[7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2*H*-1,4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione, is *N*-phenylphthalimide herbicide currently registered for pre- and post-emergent weed control on a variety of agricultural crops, including fruits, vegetables, and tree nuts; ornamentals; non-crop areas; bare-ground areas; and in aquatic settings. Flumioxazin inhibits the enzyme protoporphyrinogen oxidase, which is responsible for heme and chlorophyll production.

Flumioxazin is formulated as wettable powder (WP), dry flowable (DF), granular (G), emulsion concentrate (EC), and water dispersible granule (WDG) formulations. Flumioxazin is applied via groundboom, aerial, rotary spreader, drop spreader, chemigation, and handheld equipment. Occupational exposure to flumioxazin is expected to be short- and intermediate-term for occupational handlers, and short-term for residential handlers.

Flumioxazin causes hematological effects, including anemia and alterations in hemoglobin parameters, and liver and cardiovascular system effects in subchronic and chronic toxicity studies. Increased renal toxicity in male rats was also reported following chronic exposure.

Developmental effects were observed in rat developmental toxicity studies but not in rabbit developmental toxicity studies. Increased quantitative susceptibility, including fetal effects observed in the absence of maternal toxicity, was seen in the rat oral and dermal developmental toxicity studies, and in the rat oral reproduction toxicity study. Severe fetal effects were observed at lower doses than milder parental effects. Although there was an increase in susceptibility, HED's degree of concern for the susceptibility observed in the rat developmental and reproductive studies is low, because the regulatory endpoints for flumioxazin are based on clear NOAELs for developmental and offspring effects that are protective of the increased susceptibility seen in the developmental and reproduction studies, and there are no residual concerns for these effects. HED concluded that the 10x FQPA Safety Factor could be reduced to 1x for oral exposures.

For inhalation exposure, a rat developmental toxicity study was used to select the dose and endpoint for risk assessment (no observed adverse effect level; NOAEL of 3 mg/kg/day) based on cardiovascular effects, specifically ventricular septal defects, in fetuses at the lowest observed

adverse effect level (LOAEL) of 10 mg/kg/day. For dermal exposure, a rat dermal developmental toxicity study was used to select the dose and endpoint for risk assessment (NOAEL of 30 mg/kg/day) based on adverse cardiovascular effects in fetuses seen at the LOAEL of 100 mg/kg/day. The level of concern (LOC) for dermal and inhalation exposures is a Margin of Exposure (MOE) $\leq$100.

Inhalation exposure was assessed for both occupational and residential handlers using a point of departure (POD) extrapolated from an oral study. All occupational and residential inhalation exposure risk estimates for flumioxazin are not of concern to HED (LOC $\geq$100), and range from 610 to 244,000 for currently registered uses based on previous risk assessments conducted prior to 2012. The inhalation MOEs for the proposed uses range from 210 to 51,000 for occupational handlers and from 22,000 to 18,000,000 for residential handlers based on the most recent 2012 occupational and residential Standard Operating Procedures (SOPs), assumptions and methodology. Mixing/loading DFs for application to field peas, flax, sunflowers, safflower, and lentils provide the highest inhalation exposure to flumioxazin, with an exposure estimate (MOE) of 210 (LOC=100). The proposed labels do not require personal protection equipment (PPE) or engineering controls to reduce inhalation exposure.

III. INHALATION 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 sensitive. 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. Flumioxazin has a low vapor pressure 2.41×10^{-6} mm Hg at 22°C) and Henry's law constant (6.2×10^{-7} atm-m^3-mol^{-1}). 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 exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. It is, however, acknowledged that airblast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may contribute to spray drift. In the case of the most recent flumioxazin risk assessment, mixing/loading DFs without a respirator for aerial application to field peas, flax, sunflowers, safflower, and lentils provided the highest occupational inhalation exposure (MOE = 210).

3. **Margins of Exposure (MOEs):** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and are considered as part of the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the LOC will be considered in combination with other factors discussed here. Occupational exposure estimates (MOEs) from flumioxazin use are as low as 210 for mixing/loading DFs for aerial application (LOC=100) (M. Hawkins, May 2012. Flumioxazin: Occupational and Residential Exposure Assessment for A Proposed Use on Field Peas, Flax, Lentils, Sunflower, Safflower, and Wheat D391784) However, the majority of the occupational flumioxazin scenarios resulted in exposure risk estimates (MOEs) that were >1,000. Based on assumptions provided in the updated (2012) Residential Standard Operating Procedures (SOPs), all of the residential handler inhalation exposure risk estimates (MOEs) were >1,000 [2,700 – 244,000 based on previous risk assessments and 22,000 to 18,000,000 based on updated Residential SOPs].

4. **Toxicity:** Flumioxazin exhibits mild or low acute toxicity (Categories III or IV) via the oral, dermal, and inhalation routes. It is not an eye or skin irritant, or a dermal sensitizer. Flumioxazin produces hematological effects, including anemia and alterations in hemoglobin parameters, and cardiovascular and liver effects from subchronic chronic exposure. Developmental effects were observed in rat developmental toxicity studies but not in rabbit developmental toxicity studies. Increased renal toxicity in male rats was also reported following chronic exposure. Currently, the inhalation and dermal PODs are based on adverse fetal effects that occur in the absence of maternal toxicity. The dermal POD is based on a dermal developmental study, while the inhalation POD is based on an oral developmental study. The oral developmental toxicity studies only measure toxicity of flumioxazin after first-pass liver metabolism and do not address the concern for the potential for greater flumioxazin-induced toxicity to the developing fetus when directly entering the lung (via inhalation) and more rapidly entering the blood stream by bypassing the liver.

   When considering a waiver request for inhalation toxicity study, the Agency will evaluate other pesticides which share the same MOA and/or are in the same class. These pesticides can provide important information with respect to potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive, an inhalation toxicity study may be required regardless of MOE, depending on

the exposure profile. Flumioxazin is a dicarboximide herbicide and a member of the *N*-phenylphthalimide pesticide class. Based on a search of the Integrated Structure, Toxicology, Endpoints and Properties (ISTEP) database, flumiclorac pentyl is the only other registered *N*-phenylphthalimide pesticide. However, an inhalation toxicity study is not available for flumiclorac pentyl.

IV. HASPOC RECOMMENDATIONS:

The HASPOC concludes, based on a WOE approach, that a rat developmental inhalation toxicity study (Guideline No. 870.3700a), is required at this time. This study should include an evaluation of the respiratory tract and should follow the procedures described in Guideline No. 870.3465. This approach considered the available hazard and exposure information for flumioxazin, including (1) the observed concern for the quantitative susceptibility of the developing fetus following both oral and dermal exposure; (2) the severity of the fetal effects (ventricular septal defects) observed in the oral and dermal developmental studies; (3) that the oral developmental toxicity studies only measure toxicity of flumioxazin after first-pass liver metabolism and do not address the concern for the potential for greater flumioxazin-induced toxicity to the developing fetus when directly entering the lung (via inhalation) and more rapidly entering the blood stream by bypassing the liver; and (4) the concern for the inhalation MOE of 210 for mixing/loading DFs for application to field peas, flax, sunflowers, safflower, and lentils (and the inhalation MOE of 610 for the currently registered aquatic use).

In the absence of a route-specific inhalation developmental study, the HASPOC recommends that a 10X database uncertainty factor be applied only to assess risks for inhalation exposure scenarios for both occupational and residential use patterns.