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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 15 March 2006

SUBJECT: **Flumioxazin. Human Health Risk Assessment for the Proposed Food Use of the Herbicide Flumioxazin on Pome Fruit, Stone Fruit, and Strawberries (and for a Proposed Section 18 Exemption for Use on Alfalfa in Arizona).**

Petition Numbers:	**4F6829, 4E6845, 04AZ02**
PC Code:	**129034**
DP Numbers:	**325360, 307333**
Regulatory Citation:	**40CFR §180.568**
Chemical Class:	**N-phenylphthalimide Herbicide**
Trade Names:	**Valor™, Chateau™**

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1.0 Executive Summary

Flumioxazin, an herbicide with CAS Number 103361-09-7 and CAS Name 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 a member of the N-phenylphthalimide class of compounds. Valent USA Corporation and IR-4 have submitted petitions supporting the use of flumioxazin, as water-dispersible granule (WDG) formulations comprised of 51% active ingredient (ai), on pome fruit and stone fruit (requested by Valent in PP#4F6829), and strawberries (requested by IR-4 in PP#4E6845). Additionally, the state of Arizona has proposed a Section 18 exemption (04AZ02) for the use of flumioxazin (51% WDG) on alfalfa to control common groundsel (*senecio vulgaris*). In conjunction with the Section 3 uses, the petitioners are proposing permanent tolerances for residues of flumioxazin at 0.10 ppm in/on strawberries, and at 0.02 ppm in/on pome fruit and stone fruit. In conjunction with the Section 18 use, Arizona is proposing time-limited tolerances of 0.20 ppm in/on alfalfa forage, and 0.50 ppm in/on alfalfa hay.

1.1 Hazard and Dose Response Assessment

The toxicology database is sufficiently complete to choose endpoints for risk assessment. The scientific quality is relatively high, and the toxicity profile can be characterized for all effects, including developmental and reproductive toxicity. There is increased quantitative susceptibility of rats (but not rabbits) following *in utero* and postnatal exposure to flumioxazin.

HED evaluated the available hazard and exposure data for flumioxazin, and recommended that the Special FQPA Safety Factor (as required by the Food Quality Protection Act of August 3, 1996) be reduced from 10X to 1X for all population subgroups at all exposure durations (acute and chronic) in assessing the risk posed by this chemical. Although increased prenatal and postnatal quantitative susceptibility was seen in rats, it was concluded that there is low concern, with no residual uncertainties for pre- and/or postnatal toxicity because:

(a) developmental toxicity NOAELs/LOAELs are well characterized after oral and dermal exposure,

(b) offspring toxicity NOAEL/LOAEL are well characterized,

(c) there is a well-defined dose-response curve for the cardiovascular effects seen following oral exposure (critical period) and,

(d) the endpoints of concern are used for overall risk assessments for appropriate route and population subgroups.

Flumioxazin has mild or no acute toxicity (categories III or IV) when administered orally, dermally, or by inhalation. It has little or no toxicity (categories III or IV) with regard to eye irritation or skin irritation. The chemical was not a dermal sensitizer.

A NOAEL of 30.0 mg/kg/day was selected by HED from a rat dermal developmental toxicity study for short- and intermediate-term dermal assessments. The NOAEL was based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defects, at the LOAEL of 100 mg/kg/day. Since the dermal endpoints were based on dermal studies, an absorption factor was not required for dermal assessments.

For short-term inhalation exposure, a NOAEL of 3.0 mg/kg/day was selected by HED from an oral developmental study in rats, based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defects, at 10 mg/kg/day. For intermediate-term inhalation exposure, a NOAEL of 2.0 mg/kg/day was selected from a 2-year chronic rat study, based on increased chronic nephropathy in males, and decreased hematological parameters in females.

An acute reference dose (RfD) of 0.03 mg/kg/day was identified, based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defects. The 10X Special FQPA Safety Factor has been reduced to 1X. Therefore, the acute population

adjusted dose (aPAD) is 0.03 mg/kg/day for females 13-49, the only population subgroup of concern.

A chronic RfD of 0.02 mg/kg/day was identified, based on decreased hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) in females, and increased chronic nephropathy in males. The 10X Special FQPA Safety Factor has been reduced to 1X. Therefore, the chronic population adjusted dose (cPAD) is 0.02 mg/kg/day for all populations.

(For more detailed information, refer to *Petition Number 1F06296: Human Health Risk Assessment for the Use of the Herbicide Flumioxazin on Cotton*; D284045; William T. Drew et al; 5/24/2004.)

1.2 Residue Chemistry

Based on adequate corn, sugarcane, grape, hen, and goat metabolism data, the nature of flumioxazin in plants and animals is understood. In primary and rotated crops, the residue of concern is the parent compound only. For ruminants, the residues of concern are parent, 3-OH-flumioxazin, 4-OH-flumioxazin, plus Metabolites B, C, and F. For poultry, the residues of concern are parent, 3-OH-flumioxazin, 4-OH-flumioxazin, and 4-OH-S-53482-SA.

All of the crop field trial and processing studies are supported by adequate storage stability data and method validation data. An adequate method, utilizing gas chromatography with nitrogen-phosphorus detection (GC/NPD), is available for enforcing tolerances of flumioxazin in plant commodities (Valent Method #RM-30A-1). The reported method limit of quantitation (LOQ) and reported limit of detection (LOD) for residues of flumioxazin in plant commodities are 0.020 and 0.010 ppm, respectively.

The available field trial data are adequate, and support the proposed use patterns for flumioxazin on alfalfa, strawberries, pome fruit, and stone fruit. The number and geographic distribution of the field trials are adequate, and the appropriate samples were collected at the proposed pre-harvest intervals (PHIs). In the strawberry field trials, residues of flumioxazin were <0.020 to 0.050 ppm in annual-type strawberries harvested 1 to 2 days following a single late-season, soil-directed application of flumioxazin (51% WDG) at a rate of roughly 0.096 pounds of ai per acre (lb ai/A), 1X the proposed use rate. Following the combination of a dormant-season foliar broadcast application, and a late-season soil-directed application of flumioxazin (51% WDG) totaling approximately 0.192 lb ai/A (1X rate), residues of flumioxazin were <0.020 to 0.034 ppm in perennial-type strawberries harvested 1 day after the last application.

In the pome fruit and stone fruit field trials, flumioxazin, as either a 42% ai flowable concentrate (FC) or a 51% WDG formulation, was applied to the orchard floor as two broadcast soil applications made at a rate of 0.37 to 0.40 lb ai/A per application (at approximately 4 and 2 months prior to normal crop harvest), for a total use rate of 0.74 to 0.79 lb ai/A per season (roughly 1X the proposed maximum seasonal use rate). Residues of flumioxazin were non-detectable in all samples of pears, apples, peaches, plums, and cherries harvested at roughly 60 days after the last application.

In the alfalfa field trials, two applications of flumioxazin (51% WDG) were made at a rate of 0.125 lb ai/A per application. The initial treatment was made at 25 ± 1 days before the first cutting, and the second was made at 7 ± 1 days after the first cutting. Alfalfa forage samples were harvested 24 to 25 days after the first cutting; some of the forage was allowed to sun-dry for 3 to 8 days before the resultant hay samples were taken. Flumioxazin residues in forage ranged from 0.03 to 0.16 ppm, while residues in hay ranged from 0.06 to 0.36 ppm. (Subsequent to these field trials, Valent and Arizona proposed that the use on alfalfa be restricted to a single treatment of flumioxazin at a rate of 0.125 lb ai/A, applied no later than 10 days after the first

cutting, in order to prevent flumioxazin residues from reaching quantifiable levels in ruminant livestock commodities.)

Adequate processing studies on apples (for the processed commodities, apple juice and wet pomace) and plums (for the processed commodity, prunes) were conducted. Based on the results of field trial data at the 2X exaggerated rate, separate tolerances on the processed commodities are not required.

The regulated animal feed items associated with the proposed uses are wet apple pomace, alfalfa forage, and alfalfa hay, which are utilized in ruminant diets; alfalfa meal is utilized in poultry diets. HED concludes that there is no reasonable expectation that quantifiable residues of flumioxazin will occur in livestock commodities from the proposed uses (40CFR §180.6[a][3]). However, a cattle feeding study has been requested for confirmatory purposes, as potential residues in ruminant livestock commodities may be approaching quantifiable levels. Valent is currently conducting a ruminant feeding study in cattle.

An adequate confined rotational crop study is available to support the use on strawberries, which is the only rotated crop proposed in these petitions. Based on the results of the confined accumulation study, HED concludes that the current rotational crop plant-back intervals (PBIs) are acceptable, and that neither field trials nor tolerances for rotated crops are necessary.

There are currently no CODEX, Canadian, nor Mexican maximum residue limits (MRLs) established for flumioxazin on any commodities.

1.3 Dietary Risk Estimates from Food Sources

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the USDA's *Continuing Surveys of Food Intakes by Individuals* (CSFII) from 1994 to 1996, and 1998. The analyses were performed to support the requested Section 3 registration of flumioxazin on all of the proposed commodities.

For both the acute and chronic analyses, tolerance-level residues were assumed for all food commodities with current or proposed flumioxazin tolerances, and it was assumed that all of the crops included in the analyses were treated. These assumptions result in highly conservative estimates of dietary exposure and risk. The contribution to dietary exposure arising from residues of flumioxazin and its degradates in surface and ground water sources of drinking water were also included in the acute and chronic dietary exposure analyses. In calculating dietary risk estimates, HED has compared the aPAD and cPAD to the estimated dietary exposures from the models. Typically, HED has concerns regarding dietary risk when the exposure estimates exceed 100% of the PAD. Even with the conservative assumptions noted above, risk estimates associated with dietary exposure to flumioxazin are less than 9% of the aPAD and less than 19% of the cPAD. They are therefore below HED's level of concern for the general US population as well as all population subgroups, including those comprised of infants and children.

1.4 Dietary Risk Estimates from Drinking Water

The estimated drinking water concentrations (EDWCs) used for the cotton risk assessment also cover the proposed uses considered in this risk assessment. (Refer to *EFED Section 3 Registration for Flumioxazin to be Used on Cotton, Sugarcane, Almonds, Grapes, Christmas and Deciduous Trees, and Container- and Field-Grown Ornamentals*; D272504, D274658, and D284048; N.E. Federoff and L. Liu; 8/14/2003.)

1.5 Residential Exposure and Risk Estimates

Flumioxazin is not intended for use in public or residential settings. Therefore, residential exposure is not expected, and no residential risk assessment was performed.

1.6 Aggregate Exposure and Risk Assessment/Characterization

The contribution to dietary exposure arising from residues of flumioxazin and its degradates in surface and ground water sources of drinking water were included in the acute and chronic dietary exposure analyses described above (in Section 1.3). Because there are no residential uses, the aggregate exposure and risk are equivalent to those from dietary exposure.

1.7 Occupational Exposure and Risk Estimates

Workers may be exposed to flumioxazin during mixing, loading, and application activities associated with agricultural crops. No chemical-specific data were available with which to assess potential exposure to pesticide handlers, so estimates of exposure to pesticide handlers are based upon surrogate study data available in the *Pesticide Handler's Exposure Database* (PHED), Version 1.1 of August 1998. Defaults established by the Health Effects Division (HED) Science Advisory Council for Exposure (ExpoSAC) were used for acres treated per day and body weight.

A margin of exposure (MOE) of 100 or more is sufficient to protect occupational pesticide handlers. Occupational handler assessments indicate that all MOEs are above the levels of concern at the baseline level (total MOEs = 810 to 22,000). Post-application MOEs for alfalfa and strawberry are also above the levels of concern (530 to 8,000) on the day of application. The post-application MOEs for pome fruit and stone fruit were not determined because the herbicide is applied as a band to the orchard floor (pre-transplant or pre-emergence applications, hooded or shielded spray), and the exposures to flumioxazin for workers performing post-application activities are expected to be negligible. The 12 hour restricted entry interval (REI) appearing on the label is appropriate for this chemical.

1.8 Regulatory Recommendations and Proposed Tolerances

No major deficiencies were noted in the subject petitions that would preclude the establishment of permanent or time-limited tolerances for flumioxazin on the proposed commodities. HED has examined the residue chemistry database for flumioxazin, and recommends in favor of establishing said tolerances (with several recommended changes, as listed below).

Residue data support (and HED recommends) establishing permanent (Section 3) tolerances for residues of the herbicide flumioxazin at 0.07 ppm in/on strawberries (as generated by the NAFTA Tolerance/MRL Harmonization spreadsheet), and 0.02 ppm (the LOQ) in/on the pome fruit (Crop Group 11) and stone fruit (Crop Group 12) crop groups. Residue data support (and HED recommends) establishing time-limited (Section 18) tolerances for residues of flumioxazin at 0.13 ppm in/on alfalfa forage, and 0.45 ppm in/on alfalfa hay (as generated by the NAFTA Tolerance/MRL Harmonization spreadsheet).

The proposed tolerances should be revised to reflect the tolerances recommended by HED, and the correct commodity definitions as specified in Table 1.8 (below). To reflect the changes therein, the petitioners should also submit revised Sections F for PP#4F6829 and PP#4E6845.

TABLE 1.8 Tolerance Summary for Flumioxazin.

Crop Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct Commodity Definition*
Strawberry	0.10	0.07	*Strawberry*
Fruit, Pome, Crop Group 11	0.02	0.02	*Fruit, Pome, Group 11*
Fruit, Stone, Crop Group 12	0.02	0.02	*Fruit, Stone, Group 12*
Alfalfa Forage	0.20	0.13	*Alfalfa, Forage*
Alfalfa Hay	0.50	0.45	*Alfalfa, Hay*

2.0 Ingredient Profile

Flumioxazin is an herbicide of the N-phenylphthalimide class (Group 14) that is currently used for pre- and post-emergence control of susceptible weeds in a variety of fruit, vegetable and other field crops. Its mode of action is as an inhibitor of protoporphyrinogen oxidase (PPO); it is active against certain grasses, broadleaf weeds, and sedges. Tolerances are currently established for residues of the herbicide flumioxazin in/on various plant commodities, at levels ranging from 0.02 to 0.70 ppm (in 40CFR §180.568[a]). There are currently no CODEX, Canadian, nor Mexican maximum residue limits (MRLs) established for flumioxazin on any commodities. The chemical structure and nomenclature of flumioxazin are presented below (see Table 2.2), along with the physicochemical properties of the technical grade of flumioxazin (see Table 2.3).

2.1 Summary of Proposed Uses

Valent has submitted a petition (PP#4F6829) proposing the use of flumioxazin, formulated as two 51% WDGs (Valor™ and Chateau™ Herbicides, with EPA Registration Numbers 59639-99 and 59639-119, respectively), via broadcast applications to the orchard floor (soil) in stone fruit and pome fruit orchards. The proposed use on pome and stone fruit is for up to two applications (during the growing season) at a rate of up to 0.3825 lb ai/A per application, for a total maximum use rate of 0.765 lb ai/A per season, with a 60-day PHI, and a minimum re-treatment interval (RTI) of 30 days.

IR-4 has submitted a petition (PP#4E6845) proposing the use of a 51% WDG flumioxazin formulation (Valor™ Herbicide, with EPA Registration Number 59639-99) as a single late-season, post-emergence, post-directed (shielded) soil application to row middles (between the rows) on annual-type strawberries. The application would be made during fruit development, at a rate of up to 0.096 lb ai/A, with a PHI of 1 day. The use on perennial-type strawberries allows for an additional foliar broadcast application (during dormancy) to strawberry plants at a rate of up to 0.096 lb ai/A, resulting in a maximum seasonal use rate of 0.192 lb ai/A.

The state of Arizona has submitted a field trial study supporting their proposed Section 18 exemption for the use of 51% WDG flumioxazin (Valor™ Herbicide, EPA Registration Number 59639-99) on alfalfa, in order to control common groundsel (*senecio vulgaris*). The proposed use on alfalfa is for one foliar broadcast application at a rate of up to 0.125 lb ai/A, made no later than 10 days after the first cutting.

In conjunction with these uses, the petitioners are proposing the following tolerances:

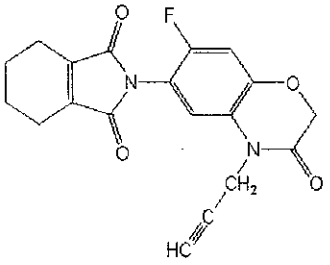
Strawberry	0.10 ppm,
Fruit, pome, crop group 11	0.02 ppm,
Fruit, stone, crop group 12	0.02 ppm,
Alfalfa forage	0.20 ppm,
Alfalfa hay	0.50 ppm.

There are currently three flumioxazin end-use products (EPs) registered to Valent in the US for use on food and/or feed crops. These EPs are marketed under the trade names Gangster™ Herbicide and Valor™ Herbicide, both of which are 51% wettable powders (WPs), with EPA Registration Numbers 59639-98 and 59639-131, respectively. Valor™ is also formulated as a 51% WDG (EPA Registration Number 59639-99). For the proposed uses on strawberries and alfalfa, IR-4 and Arizona (respectively) are supporting the use of Valor™ 51% WDG. For the proposed uses on stone and pome fruit, Valent is supporting the use of Valor™ 51% WDG, along with a new 51% WDG, Chateau™ Herbicide (EPA Registration Number 59639-119). Example labels were provided, and the use directions for alfalfa, strawberries, stone fruit, and pome fruit are summarized below (see Table 2.1). The proposed use directions adequately reflect the use patterns as applied in the alfalfa, strawberry, pome fruit, and stone fruit field trials.

TABLE 2.1 Summary of Use Directions for Flumioxazin.					
Application Type, Timing, and Equipment [1]	**Formulation [EPA Registration Number]**	**Single Use Rate (lb ai/A)**	**Maximum Number of Applications per Season**	**Maximum Seasonal Use Rate (lb ai/A)**	**PHI (Days)**
Alfalfa					
Foliar broadcast, up to 10 days after first cutting.	51% WDG [59639-99]	0.125	1	0.125	25
Strawberry (Annual) [2]					
Soil-directed application, during fruit development.	51% WDG [59639-99]	0.096	1	0.096	1
Strawberry (Perennial) [2]					
Foliar broadcast application, during dormancy.	51% WDG [59639-99]	0.096	2	0.192	1
Soil-directed application, during fruit development.					
Pome Fruit (Crop Group 11) [3]					
Broadcast soil application, at roughly 120 and 60 days prior to normal crop maturity.	51% WDG [59639-99] [59639-119]	0.3825	2	0.765	60
Stone Fruit (Crop group 12) [3]					
Broadcast soil application, at roughly 120 and 60 days prior to normal crop maturity.	51% WDG [59639-99] [59639-119]	0.3825	2	0.765	60

1. Applications via ground equipment to pre- or post-emergence weeds; for pre-plant burndown, aerial equipment can be used; do not apply through any type of irrigation system.
2. Annual strawberry plants are planted in fall and harvested for only one season, whereas perennial strawberry plants are maintained and harvested over several years.
3. The proposed minimum re-treatment interval (RTI) for use on pome and stone fruit is 30 days.

2.2 Structure and Nomenclature

TABLE 2.2 Flumioxazin Nomenclature.	
Compound	
Common Name	Flumioxazin
Empirical Formula	$C_{19}H_{15}FN_2O_4$
Company Experimental Name	VC-1152
IUPAC Name	*N*-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboxamide
CAS Name	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
CAS Registry Number	103361-09-7
Chemical Class	N-phenylphthalimide herbicide
Known Impurities of Concern	None
End-Use Products (EPs)	Valor™ WDG, Chateau™ WDG

2.3 Physical and Chemical Properties

TABLE 2.3 Physicochemical Properties of Flumioxazin.[1]	
Parameter	**Value**
Melting Point/Range (°C)	202-204
pH at 25°C	7.29
Density at 20°C (g/mL)	1.51
Water Solubility at 25°C (mg/L)	1.79
Solvent Solubility	NA[2]
Vapor Pressure (mm Hg)	2.41×10^{-6}
Dissociation Constant (pK_a)	NA (does not dissociate)
Octanol/Water Partition Coefficient at 20°C (Log [K_{OW}])	2.55
UV/Visible Absorption Spectrum	8_{218}, , = 14700 (pH 1.9) 8_{216}, , = 43600 (pH 6.8) 8_{216}, , = 51200 (pH 10.0)

1. Data obtained from US EPA Pesticide Fact Sheet for flumioxazin, issued on 4/12/2001 for conditional registration (http://www.epa.gov/opprd001/factsheets/flumioxazin.pdf).
2. NA = Not Available.

3.0 Metabolism Assessment

The nature of the residue has been adequately delineated for both plant and animal commodities. In plants, the major metabolic pathway is hydrolysis of the imide moiety to produce the metabolites THPA and APF. The THPA is then hydrated to produce 1-OH-HPA. The residue of concern in plants, for both tolerance expression and risk assessment purposes, is the parent compound only.

The results of the ruminant and poultry metabolism studies with both phenyl- and THP-labeled flumioxazin show that the major metabolic pathways are hydrolysis of the imide moiety, hydroxylation of the cyclohexene ring, and the equivalent of addition of sulfonic acid to the alkene function. The residues of concern in ruminants are the parent, 3-OH-flumioxazin, 4-OH-flumioxazin, and metabolites B, C, and F. In poultry, the residues of concern are parent, 3-OH-flumioxazin, 4-OH-flumioxazin, and 4-OH-S-53482-SA.

(For more detailed information, refer to *Petition Number 1F06296: Human Health Risk Assessment for the Use of the Herbicide Flumioxazin on Cotton*; D284045; William T. Drew et al; 5/24/2004.)

4.0 Hazard Characterization/Assessment

The toxicology database is sufficiently complete to choose endpoints for risk assessment. The scientific quality is relatively high, and the toxicity profile can be characterized for all effects, including developmental and reproductive toxicity. There is increased quantitative susceptibility of rats (but not rabbits) following *in utero* and postnatal exposure to flumioxazin.

Flumioxazin has mild or no acute toxicity (categories III or IV) when administered orally, dermally, or by inhalation. It has little or no toxicity (categories III or IV) with regard to eye irritation or skin irritation. The chemical was not a dermal sensitizer.

A NOAEL of 30.0 mg/kg/day was selected by HED from a rat dermal developmental toxicity study for short- and intermediate-term dermal assessments. The NOAEL was based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defects, at the LOAEL of 100 mg/kg/day. At a dose of 300 mg/kg/day, there was statistical significance for the ventricular septal defects as well as increased resorptions, decreased number of viable fetuses, decreased fetal body weight, increased incidence of wavy ribs and decreased

numbers of ossified sacrococcygeal vertebral bodies. Since the dermal endpoints were based on dermal studies, an absorption factor was not required for dermal assessments.

For short-term inhalation exposure, a NOAEL of 3.0 mg/kg/day was selected by HED from an oral developmental study in rats, based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defects, at 10 mg/kg/day. At 30 mg/kg/day statistical significance was achieved for these observations and the following additional findings were noted: increased resorptions, decreased number of viable fetuses, decreased fetal body weight, increased abnormalities of the ribs (wavy) as well as scapula (curvature) and decreased numbers of ossified sacrococcygeal vertebral bodies. For intermediate-term inhalation exposure, a NOAEL of 2.0 mg/kg/day was selected from a 2-year chronic carcinogenicity study in rats, based on decreased hemoglobin, MCV, and MCHC in females and increased chronic nephropathy in males.

An acute RfD (0.03 mg/kg/day) was identified, based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defects. The 10X Special FQPA Safety Factor has been reduced to 1X. Hence, for dietary risk assessments, the acute population adjusted dose (aPAD) is 0.03 mg/kg/day for females 13-49, the only population subgroup of concern.

A chronic RfD (0.02 mg/kg/day) was identified, based on decreased hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) in females, and increased chronic nephropathy in males. The 10X Special FQPA Safety Factor has been reduced to 1X. Consequently, for dietary risk assessments, the chronic population adjusted dose (cPAD) is 0.02 mg/kg/day for all populations.

(For more detailed information, refer to *Petition Number 1F06296: Human Health Risk Assessment for the Use of the Herbicide Flumioxazin on Cotton*; D284045; William T. Drew et al; 5/24/2004.)

TABLE 4.0 Summary of Toxicological Doses and Endpoints for Flumioxazin Used in the Human Health Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary Females 13-49	NOAEL = 3 mg/kg/day UF = 100 **Acute RfD** = NOAEL ÷ UF = 0.03 mg/kg/day	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.03 mg/kg/day	**Oral Developmental and Supplemental Prenatal Studies (Rat)** LOAEL = 10 mg/kg/day, based on cardiovascular effects (especially ventricular septal defects in fetuses).
Acute Dietary General Population	An endpoint attributable to a single dose (exposure) was not identified from the available studies, including the developmental toxicity studies in rats and rabbits.		
Chronic Dietary All Populations	NOAEL = 2 mg/kg/day UF = 100 **Chronic RfD** = NOAEL ÷ UF = 0.02 mg/kg/day	FQPA SF = 1 **cPAD** = chronic RfD / FQPA SF = 0.02 mg/kg/day	**2-Year Chronic/Carcinogenicity Study (Rat)** LOAEL = 18 mg/kg/day, based on increased chronic nephropathy in males and decreased hematological parameters in females (Hgb, MCV, MCH, and MCHC).

TABLE 4.0 Summary of Toxicological Doses and Endpoints for Flumioxazin Used in the Human Health Risk Assessment.			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral (Short- and Intermediate-Term)	NOAEL = 6.3 mg/kg/day	Target MOE = 100 (Occupational) Target MOE = 1000 (Residential)	**2-Generation Reproduction Study (Rat)** LOAEL = 12.7 mg/kg/day, based on decreased pup body weight and testicular atrophy in F1 males.
Dermal (All Durations)	NOAEL = 30 mg/kg/day	Target MOE = 100 (Occupational) Target MOE = 1000 (Residential)	**Dermal Developmental Study (Rat)** LOAEL = 100 mg/kg/day, based on cardiovascular effects (especially ventricular septal defects in fetuses).
Short-Term Inhalation	NOAEL = 3 mg/kg/day	Target MOE = 100 (Occupational) Target MOE = 1000 (Residential)	**Oral Developmental Study (Rat)** LOAEL = 10 mg/kg/day, based on cardiovascular effects (especially ventricular septal defects in fetuses).
Intermediate- and Long-Term Inhalation	NOAEL = 2 mg/kg/day	Target MOE = 100 (Occupational) Target MOE = 1000 (Residential)	**2-Year Chronic/Carcinogenicity Study (Rat)** LOAEL = 18 mg/kg/day, based on increased chronic nephropathy in males and decreased hematological parameters in females (Hgb, MCV, MCH, and MCHC).
Cancer (Oral, Dermal, Inhalation)	"**Not likely to be a carcinogen for humans**," based on the lack of carcinogenicity in a 2-year rat study, an 18-month mouse study, and a battery of mutagenic studies.		

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA. Residential target MOEs are 1000 because there are no proposed residential uses, and therefore the 10X safety factor decision made previously was not reevaluated.

UF = Uncertainty Factor.
FQPA SF = special FQPA Safety Factor.
NOAEL = No Observed Adverse Effect Level.
LOAEL = Lowest Observed Adverse Effect Level.
PAD = Population Adjusted Dose (a = acute, c = chronic).
RfD = Reference Dose.

5.0 Public Health Data

The OPP Incident Data System (7/23/2003) indicates that in 2002 there were 14 reported incidents, involving 1 minor human incident, 1 domestic animal incident, 6 for minor plant damage, and 6 for minor property damage.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

The submitted crop field trial data for alfalfa, strawberry, pome fruit, and stone fruit are adequate to support the proposed uses on the requested commodities. A method utilizing GC/NPD is available for enforcing tolerances of flumioxazin in plant commodities (Valent Method #RM-30A-1). The reported method LOQ and reported LOD for residues of flumioxazin

in plant commodities are 0.020 and 0.010 ppm, respectively. Residues of flumioxazin in samples from the current alfalfa, strawberry, pome fruit, and stone fruit field trials (and the associated processing studies) were determined using the enforcement method cited above, and/or another adequate GC/NPD method (Valent Method #RM-30A-3) that is a more recent version of the enforcement method. For Method #RM-30A-3 the validated LOQ for flumioxazin residues is 0.020 ppm in alfalfa, strawberries, pome fruit, and stone fruit; the LOQ is 0.005 ppm in apple juice. The LOD is 0.010 ppm in alfalfa, pome fruit, and stone fruit, 0.004 ppm in strawberries, and 0.003 ppm in apple juice and wet pomace.

Residues of flumioxazin were less than 0.020 ppm in all samples of pome fruit and stone fruit harvested roughly 60 days following the last of two broadcast soil applications of flumioxazin (42% FC or 51% WDG formulations) made at total seasonal rates of 0.74 to 0.79 lb ai/A. Since flumioxazin is applied directly to the soil, and the proposed PHI for pome and stone fruit is 60 days, residue decline data are not required to support the proposed use on either pome fruit nor stone fruit.

Following a single late-season application of flumioxazin (51% WDG) at a rate of 0.094 to 0.096 lb ai/A, residues of flumioxazin were <0.020 to 0.050 ppm in 10 samples of annual-type strawberries harvested 1 to 2 days after the last application. Following a dormant-season application and a late-season application of flumioxazin, at a total rate of 0.192 lb ai/A, residues of flumioxazin were <0.020 to 0.034 ppm in 6 samples of perennial-type strawberries harvested 1 day after the last application. Residue decline studies were not conducted.

In the alfalfa field trials, two applications of flumioxazin (51% WDG) were made at a rate of 0.125 lb ai/A per application. The initial treatment was made at 25 ± 1 days before the first cutting, and the second was made at 7 ± 1 days after the first cutting. Alfalfa forage samples were harvested 24 to 25 days after the second treatment; some of the forage was allowed to sun-dry for 3 to 8 days before the resultant hay samples were taken. Flumioxazin residues in forage samples ranged from 0.03 to 0.16 ppm, while residues in hay samples ranged from 0.06 to 0.36 ppm. Residue decline studies were not conducted. The alfalfa field trials were conducted at twice the proposed maximum seasonal application rate. HED is therefore recommending that the Section 18 tolerances on alfalfa forage and hay be established at half the levels generated by the NAFTA Tolerance/MRL Harmonization spreadsheet.

Apple and prune processing studies were conducted, although exact processing factors for processed commodities could not be calculated. In the processing studies, residues of flumioxazin were non-detectable (less than 0.010 ppm) in both apples and fresh plums, the raw agricultural commodities (RACs), harvested from trials conducted at 2X the proposed maximum seasonal use rate. Residues were also non-detectable in processed apple juice and wet pomace (less than 0.003 ppm), and dried prunes (less than 0.010 ppm). Although the processing studies were only conducted at a 2X rate, HED concludes that flumioxazin residues are unlikely to exceed 0.020 ppm (the proposed RAC tolerance) in processed apple and plum commodities, even following a 5X application rate. Therefore, separate tolerances are not required for apple juice, wet pomace, nor prunes.

New storage stability data were provided (in conjunction with the field trials and associated processing studies) indicating that flumioxazin is stable in frozen storage (-20°C) for intervals of up to 11.6 months in cherries, 8.6 months in prunes, 8.8 months in wet apple pomace, and 6.4 months in apple juice. Together with earlier storage stability data on a wide variety of plant commodities, the data cited above support the sample storage durations and conditions used in the alfalfa, strawberry, pome fruit, and stone fruit field trials, as well as the plum and apple processing studies.

The regulated animal feed items associated with the proposed uses are wet apple pomace, alfalfa forage, and alfalfa hay, which are utilized in ruminant diets; alfalfa meal is utilized in

poultry diets. Based on current and recommended tolerances, the calculated maximum theoretical dietary burden (MTDB) for flumioxazin in beef and dairy cattle is 0.316 ppm, while the MTDBs for poultry and swine are 0.063 and 0.020 ppm, respectively (see Table 6.1.1, below). Flumioxazin residues in wet apple pomace, alfalfa forage, and alfalfa hay would contribute roughly 23% of the MTDB for cattle. After considering the results of the poultry (152X) and goat (23X to 37X) metabolism studies, HED concludes that there is no reasonable expectation that quantifiable residues of flumioxazin will occur in livestock commodities from the proposed uses (40CFR §180.6[a][3]). However, a cattle feeding study has been requested for confirmatory purposes, as potential residues in ruminant livestock commodities may be approaching quantifiable levels (refer to *Petitions Numbered 0F06171, 1F06296, 3E06777, 3E06779, 3E6788: Human Health Risk Assessment for the Use of the Herbicide Flumioxazin on Sugarcane, Grape, Almond/Pistachio, Mint, Tuberous/Corm Vegetables (Crop Subgroup 1C), and Dry Bulb Onion/Garlic/Shallot.*; D268181, D284045; William T. Drew et al; 7/21/2004). Valent is currently conducting a ruminant feeding study in cattle.

TABLE 6.1.1 Calculation of MTDBs for Flumioxazin Residues in Livestock.

Feed Commodity	% Dry Matter[1]	% Diet[1]	Current or Recommended Tolerance (ppm)	Dietary Contribution (ppm)[2]
Beef and Dairy Cattle				
Almond Hulls	90	10	0.70	0.078
Cotton Gin By-Products	90	20	0.60	0.133
Sugarcane Molasses[3]	75	10	0.20	0.027
Apple Wet Pomace[3]	40	20	0.02	0.010
Cottonseed Meal[3]	89	25	0.02	0.006
Alfalfa Forage	35	10	0.13	0.037
Alfalfa Hay	89	5	0.45	0.025
TOTAL BURDEN		**100**	--	**0.316**
Poultry				
Soybean Meal[3]	NA[4]	40	0.02	0.008
Peanut Meal[3]	NA	25	0.02	0.005
Soybean Hulls[3]	NA	20	0.02	0.004
Cottonseed Meal[3]	NA	5	0.02	0.001
Alfalfa Meal[3]	NA	10	0.45	0.045
TOTAL BURDEN		**40**	--	**0.063**
Swine				
Soybean Seed	NA	50	0.02	0.010
Potato Culls[3]	NA	50	0.02	0.010
TOTAL BURDEN		**100**	--	**0.020**

1. OPPTS Residue Chemistry Test Guideline 860.1000, Table 1 (August 1996).
2. Contribution = [Tolerance ÷ %Dry Matter (for cattle)] × %Diet.
3. Tolerance levels in processed fractions are based on the tolerance of the associated RAC.
4. NA = Not Applicable.

HED notes that a much higher percentage of alfalfa hay or forage than shown in Table 6.1.1 would normally be included in the diet. For the purposes of the very limited use under the Section 18 exemption, only 5-10% is being used. For any future Section 3 registrations on alfalfa, the MTDB will be based on a higher percentage, likely resulting in an increased burden for cattle.

A confined rotational crop study is available to support the use on strawberries, which is the only rotated crop proposed in the Section 3 petitions. Based on the results of the confined accumulation study, HED concludes that the current rotational crop PBIs are acceptable, and that neither field trials nor tolerances for rotated crops are necessary.

6.1.2 Acute and Chronic Dietary Exposure and Risk

The dietary exposure assessment, entitled *Flumioxazin. Acute and Chronic Dietary Exposure Assessments for Tolerances (Associated with Section 3 Registration) on Pome Fruit (Crop Group 11), Stone Fruit(Crop Group 12), and Strawberries.*, was conducted by William T. Drew, dated 3/15/2006, with DP Number D325418.

Acute and chronic dietary risk assessments were conducted for the new uses of the active ingredient flumioxazin using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the USDA's *Continuing Surveys of Food Intakes by Individuals* (CSFII) from 1994 to 1996, and 1998. The analysis was performed to support requests for tolerances on pome fruit (Crop Group 11) , stone fruit (Crop Group 12), and strawberries.

Acute Dietary Exposure: A conservative acute dietary exposure analysis was performed for flumioxazin. The analysis is based on tolerance-level residues, and the assumption that 100% of the crop will be treated. It includes the contribution to acute dietary exposure arising from residues of flumioxazin and its degradates in surface and ground water sources of drinking water. The risk estimate for the population subgroup, females 13-49 (the only subgroup for which an acute endpoint was selected), is below HED's level of concern, utilizing 8% of the aPAD at the 95th percentile of exposure.

Chronic Dietary Exposure: A conservative chronic dietary exposure analysis was performed for flumioxazin. The analysis is based on tolerance-level residues and the assumption that 100% of the crop will be treated. It includes the contribution to chronic dietary exposure arising from residues of flumioxazin and its degradates in surface and ground water sources of drinking water. The risk estimates for all population subgroups are below HED's level of concern. The risk estimate for the general US population is 6% of the cPAD. The most highly exposed population subgroup is all infants <1, which utilizes 18% of the cPAD.

Cancer Dietary Exposure: Because HED has determined that flumioxazin is not likely to be a human carcinogen, no cancer dietary exposure analysis was conducted.

TABLE 6.1.2 Summary of Dietary Exposure and Risk for Flumioxazin.

Population Subgroup	Acute Dietary (95th Percentile)*			Chronic Dietary*		
	aPAD (mg/kg)	Exposure (mg/kg/day)	% aPAD	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General US Population	Not applicable.			0.02	0.00118	6
All Infants <1 year				**0.02**	**0.00368**	**18**
Children 1-2 years				0.02	0.00211	11
Children 3-5 years				0.02	0.00190	10
Children 6-12 years				0.02	0.00126	6
Youths 13-19 years				0.02	0.00088	4
Adults 20-49 years				0.02	0.00105	5
Adults 50+ years				0.02	0.00110	6
Females 13-49 years	**0.03**	**0.00251**	**8**	0.02	0.00105	5

* Values for the population with the highest risk for each type of risk assessment are **bolded**.

6.2 Water Exposure/Risk Pathway

The estimated drinking water concentrations (EDWCs) used for the cotton risk assessment also cover the proposed uses considered in this risk assessment. The EDWC for flumioxazin residues used in this dietary risk assessment was obtained from EFED's environmental risk assessment

for flumioxazin, *EFED Section 3 Registration for Flumioxazin to be Used on Cotton, Sugarcane, Almonds, Grapes, Christmas and Deciduous Trees, and Container- and Field-Grown Ornamentals*; D272504, D274658, and D284048; N.E. Federoff and L. Liu; 8/14/2003. The EDWC for flumioxazin residues (used in both the acute and chronic dietary analyses) was 0.048 ppm, the concentration in groundwater as estimated by the SCI-GROW model. SCI-GROW (Screening Concentration In GrOundWater) is an empirical model for predicting pesticide levels in groundwater; the value from SCI-GROW is considered an upper bound concentration estimate, and therefore conservative. The groundwater EDWC (0.048 ppm), which is greater than the surface water EDWC (0.034 ppm), was used in both the acute and the chronic dietary analyses in order to be conservative.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

Flumioxazin is not intended for use in public or residential settings. Therefore, residential exposure is not expected, and no residential risk assessment was performed.

7.0 Aggregate Risk Assessments and Risk Characterization

The acute aggregate risk is based on the sum of exposures resulting from only dietary food and drinking water exposure. This acute aggregate risk assessment was conducted for Females 13-49, the only population subgroup of concern, using the aPAD (0.03 mg/kg/day).

The chronic (non-cancer) aggregate risk is based on the sum of exposures resulting from average food exposure, plus drinking water exposure, plus long-term residential exposure. Flumioxazin has no proposed nor registered residential uses. Therefore, this risk assessment is based on the aggregate of average dietary (food) and average drinking water exposures only. This chronic aggregate risk assessment was conducted for all population subgroups, and the cPAD (0.02 mg/kg/day) was applied to all population subgroups.

The contribution to dietary exposure arising from residues of flumioxazin and its degradates in surface and ground water sources of drinking water were included in the acute and chronic dietary exposure analyses described above (in Section 6.1.2). Both the acute aggregate risk and the chronic aggregate risk are below HED's level of concern.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach, based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to flumioxazin and any other substances, and flumioxazin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that flumioxazin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs (OPP) concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

A Section 18 (emergency exemption) use, and a Section 3 (registration) use are being requested for EPs containing the herbicide flumioxazin as the sole ai. The proposed uses include the emergency use of Chateau™ Herbicide (51% WDG) on alfalfa, and registered uses of Chateau™ Herbicide and Valor™ Herbicide (51% WDGs) on pome fruit, stone fruit, and strawberries, to be applied by ground-boom.

No data regarding the number of exposure days per year were provided. However, due to the frequency of applications, EPA assumes that handlers involved in applications would be

exposed for less than 6 months per year. Thus, handler exposures are expected to be short- to intermediate-term in duration. Long-term exposures (greater than 6 months) are not expected.

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of flumioxazin, HED used surrogate data from the *Pesticide Handlers Exposure Database* (PHED), Version 1.1 of August 1998. Defaults established by the HED's ExpoSAC were used for acres treated per day and body weight.

Toxicological endpoints from the HED toxicological review report (Alan Levy, 2/22/2001) were used to assess risk. Since the dermal endpoints were based on a dermal study, a dermal absorption factor was not required for the dermal assessment, and the inhalation absorption rate was assumed to be 100%. The short-, intermediate-, and long-term dermal toxicological doses are all 30.0 mg ai/kg bw/day, based upon biologically significant cardiovascular abnormalities (particularly ventricular septal effects) seen in a rat dermal developmental study at the LOAEL of 100 mg/kg/day. The short-term inhalation dose of 3.0 mg ai/kg bw/day was based upon cardiac abnormalities seen in the rat oral developmental study at the LOAEL of 10 mg/kg/day. The intermediate- and long-term inhalation doses of 2.0 mg ai/kg bw/day were identified from a 2-year rat toxicity study, where kidney effects were seen in males, and anemia was seen in females at the LOAEL of 18 mg/kg/day. Flumioxazin is classified as "not likely to be a human carcinogen," and, therefore, a cancer risk assessment is not necessary.

Occupational handler assessments revealed that all MOEs are above the levels of concern at the baseline level (total MOEs = 810 to 22,000). Post-application MOEs for alfalfa and strawberry are also above the levels of concern (530 to 8,000) on the day of application. The post-application MOEs for pome fruit and stone fruit were not determined because the herbicide is applied as a band to the orchard floor (pre-transplant or pre-emergence application, hooded or shielded spray), and the exposures to flumioxazin for workers performing post-application activities are expected to be negligible. The 12 hour REI appearing on the label is appropriate for this chemical.

The risk assessment for non-occupational/residential handler and post-application exposures was not performed because flumioxazin is not registered for residential use.

9.1 Short/Intermediate/Long-Term Handler Risk

Workers may be exposed to flumioxazin during mixing, loading, and application activities associated with agricultural crops. Based upon the proposed use patterns, short- and intermediate-term dermal and inhalation exposure are expected to occur. HED believes the most highly exposed occupational pesticide handlers are likely to be:

(1) mixing and loading WDGs for ground-boom application, and
(2) applying sprays using an open-cab ground-boom.

For pesticide handlers, it is HED's standard practice to present estimates of dermal exposure for "baseline" (with a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, and no protective gloves), and for a single layer of work clothing and protective gloves or other Personal Protective Equipment (PPE) as might be necessary. The registered and proposed product labels involved in this assessment direct pesticide handlers to wear long-sleeved shirt, long pants, chemical resistant gloves (made of any waterproof material, such as polyethylene or polyvinyl chloride), shoes, and socks.

Since the toxicological effects were fetal effects seen in a developmental study, and hematological effects in females seen in the chronic study for inhalation, HED assumed a 60 kg body weight to calculate average daily doses of exposure. Furthermore, because both short-term dermal and inhalation endpoints are based on the same toxicological effects (cardiovascular effects), the route-specific MOEs were combined into a total MOE. However, intermediate-term

dermal and inhalation effects were based on different endpoints; therefore, a separate MOE was calculated for each route of exposure.

Assumptions and calculations of the risks for handlers are presented below (see Tables 9.1.1 and 9.1.2). All handler MOEs were above HED's level of concern at the baseline level (total MOEs = 810 to 22,000; HED's level of concern is for MOEs of 100 or less).
The handler exposure estimates in this assessment are based on a central tendency estimate of unit exposure, and an upper-percentile assumption for the application rate. They are assumed to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data (differences in use scenario and data confidence), and assumptions regarding the amount of chemical handled. The estimated exposures are believed to be reasonable high-end estimates, based on observations from field studies, and professional judgment.

TABLE 9.1.1 Short-Term Handler Exposure and Risk for Flumioxazin.

Product [Formulation]	Use Scenario	Mitigation Level	Unit Exposures (mg/lb ai)[1]		Application Rates[2] (lb ai/A)	Crop	Amount Handled per Day (A/day)[3]	Dose (mg/kg/day)[4]		Short-Term MOE[5]		
			Dermal	Inhalation				Dermal	Inhalation	Dermal	Inhalation	Total[6]
Mixer/Loader												
CHATEAU™ [51% WDG] **VALOR™** [51% WDG]	Ground-boom	Baseline	0.066	0.00077	0.125	Alfalfa	80	0.011	0.000128	2,700	23,000	2,400
					0.38	Pome/Stone Fruit		0.033	0.00039	900	7,700	810
					0.096	Strawberry		0.0084	0.000098	3,600	31,000	3,300
Applicators												
CHATEAU™ [51% WDG] **VALOR™** [51% WDG]	Ground-boom	Baseline	0.014	0.00074	0.125	Alfalfa	80	0.0023	0.000123	13,000	24,000	8,300
					0.38	Pome/Stone Fruit		0.007	0.00037	4,300	8,100	2,800
					0.096	Strawberry		0.0018	0.000093	17,000	32,000	11,000

1. Unit Exposures are taken from *PHED Surrogate Exposure Guide, Estimates of Worker Exposure* from *Pesticide Handler Exposure Database*, Version 1.1 of August 1998. Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**. Units = mg ai/pound of ai handled.
2. Application rates taken from proposed labels as cited earlier.
3. Units Treated are taken from *Standard Values for Daily Acres Treated in Agriculture* (SOP #9.1), ExpoSAC, 7/5/2000, PHED, Version 1.1 of May 1997.
4. Average Daily Dose (ADD) = Unit Exposure x Application Rate x Units Treated ÷ Body Weight (60 kg).
5. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. Short-term dermal NOAEL = 30 mg ai/kg bw/day. Short-term inhalation NOAEL = 3.0 mg ai/kg bw/day.
6. Since the toxicological effects are essentially the same (cardiovascular effects), but were identified from different studies (**dermal** developmental versus **oral** developmental), and have different NOAELs (30 versus 3.0), the MOEs are combined using the following convention: $1/[(1/MOE_{DERMAL}) + (1/MOE_{INHALATION})]$ = Aggregate MOE (HED SOP 97.2 of 11/26/1997).

TABLE 9.1.2 Intermediate-Term Handler Exposure and Risk for Flumioxazin.

Product [Formulation]	Use Scenario	Mitigation Level	Unit Exposures (mg/lb ai)[1]		Application Rates[2] (lb ai/A)	Crop	Amount Handled per Day (A/day)[3]	Dose (mg/kg/day)[4]		Intermediate-Term MOE[5]	
			Dermal	Inhalation				Dermal	Inhalation	Dermal	Inhalation
Mixer/Loader											
CHATEAU™ [51% WDG] **VALOR™** [51% WDG]	Ground-boom	Baseline	0.066	0.00077	0.125	Alfalfa	80	0.011	0.000128	2,700	15,000
					0.38	Pome/Stone Fruit		0.033	0.00039	900	5,100
					0.096	Strawberry		0.0084	0.000098	3,600	21,000
Applicators											
CHATEAU™ [51% WDG] **VALOR™** [51% WDG]	Ground-boom	Baseline	0.014	0.00074	0.125	Alfalfa	80	0.0023	0.000123	13,000	16,000
					0.38	Pome/Stone Fruit		0.007	0.00037	4,000	5,400
					0.096	Strawberry		0.0018	0.000093	17,000	22,000

1. Unit Exposures are taken from *PHED Surrogate Exposure Guide, Estimates of Worker Exposure* from *Pesticide Handler Exposure Database*, Version 1.1 of August 1998. Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**. Units = mg ai/pound of ai handled.
2. Application rates taken from proposed labels as cited earlier.
3. Units Treated are taken from *Standard Values for Daily Acres Treated in Agriculture* (SOP #9.1), ExpoSAC, 7/5/2000, PHED, Version 1.1 of May 1997.
4. Average Daily Dose (ADD) = Unit Exposure x Application Rate x Units Treated ÷ Body Weight (60 kg).
5. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ Dose. Intermediate-term dermal NOAEL = 30 mg ai/kg bw/day. Intermediate-term inhalation NOAEL = 2.0 mg ai/kg bw/day.

9.2 Short-, Intermediate-, and Long-Term Post-Application Risk

There is some potential for agricultural workers to have post-application exposures to pesticides during the growing and/or harvesting of alfalfa and strawberry. The post-application exposures/risks for pome and stone fruit were not determined because the herbicide is applied as a band to the orchard floor (pre-transplant or pre-emergence application, hooded or shielded spray; spray contact to foliage and/or green bark is avoided), and thus the exposures to flumioxazin for workers performing post-application activities are expected to be negligible.

Since no post-application data were submitted in support of this registration action, dermal exposures during post-application activities were estimated using dermal transfer coefficients from ExpoSAC's *Policy Number 3.1: Agricultural Transfer Coefficients* of August 2000, and HED's REI Calculator, as summarized in Table 9.2.1 (below), along with the following assumptions:

(1) Application Rates	=	0.125 lb ai/A for alfalfa,
	=	0.096 lb ai/A for strawberry,
(2) Exposure Duration	=	8 hours per day, and
(3) Body Weight	=	60 kg.

The fraction of ai retained on foliage is assumed to be 20% (0.2) on day zero, which equals the % dislodgeable foliar residue (DFR) after initial treatment. This fraction is assumed to further dissipate at the rate of 10% (0.1) per day on following days. These are default values established by the ExpoSAC.

Although all the activities and associated transfer coefficients have been listed for each crop in Table 9.2.1, not all scenarios are applicable since flumioxazin sprays are not always directed to crop foliage for all the proposed uses on the requested commodities.

TABLE 9.2.1 Anticipated Post-Application Activities and Dermal Transfer Coefficients.

Proposed Crops	Policy Crop Group Category	Exposure Potential	Transfer Coefficients (cm^2/hr)	Activities
Alfalfa	Field/row crop, low/medium.	Low	100	Irrigation, scouting, thinning.
		Medium	1500	Irrigation, scouting.
Strawberry	Berry, low.	Low	400	Irrigation, scouting, weeding, pruning, thinning, mulching.
		High	1500	Harvesting, hand pruning, pinching, training.

A summary of the risk and exposure during post-application activities is included in Table 9.2.2, below. All post-application exposure MOEs are above HED's level of concern on the day of application (HED's level of concern = 100).

TABLE 9.2.2 Post-Application Exposure and Risk for Flumioxazin.								
Crop	Day	DFR (ug/cm2)[1]	Daily Dose (mg/kg/day)[2]			MOE[3]		
			Low	Medium	High	Low	Medium	High
Alfalfa	0	0.28	0.0037	0.056	NA	8,000	530	NA
Strawberry	0	0.22	0.011	NA	0.043	2,600	NA	700

1. DFR_t (ug/cm^2) = Application Rate (lb ai/A) x F x (1-D)[1] x 4.54E8 Φg/lb x 24.7E-9 A/cm^2
2. Daily Dermal Dose $_t$ = [DFR_t (Φg/cm^2) x 1E-3 mg/Φg x Tc (cm^2/hr) x ET (hrs)]/BW (kg).
3. MOE = NOAEL (30 mg/kg/day)/Daily Dermal Dose.

10.0 Data Needs and Label Requirements

10.1 Toxicology

No additional toxicological studies are required for flumioxazin at this time.

10.2 Residue Chemistry

The proposed tolerances should be revised to reflect the tolerance as recommended by HED, and the correct commodity definition as specified in Table 10.2 (below). To reflect the changes therein, the petitioners should also submit revised Sections F for PP#4F6829 and PP#4E6845.

TABLE 10.2 Tolerance Summary for Flumioxazin.			
Crop Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct Commodity Definition*
Strawberry	0.10	0.07	*Strawberry*
Fruit, Pome, Crop Group 11	0.02	0.02	*Fruit, Pome, Group 11*
Fruit, Stone, Crop Group 12	0.02	0.02	*Fruit, Stone, Group 12*
Alfalfa Forage	0.20	0.13	*Alfalfa, Forage*
Alfalfa Hay	0.50	0.45	*Alfalfa, Hay*

References:

1. *EFED Section 3 Registration for Flumioxazin to be Used on Cotton, Sugarcane, Almonds, Grapes, Christmas and Deciduous Trees, and Container- and Field-Grown Ornamentals*; D272504, D274658, and D284048; N.E. Federoff and L. Liu; 8/14/2003.

2. *Petitions Numbered 0F06171, 1F06296, 3E06777, 3E06779, 3E6788: Human Health Risk Assessment for the Use of the Herbicide Flumioxazin on Sugarcane, Grape, Almond/Pistachio, Mint, Tuberous/Corm Vegetables (Crop Subgroup 1C), and Dry Bulb Onion/Garlic/Shallot.*; D268181, D284045; William T. Drew et al; 7/21/2004

3. *Petition Number 1F06296: Human Health Risk Assessment for the Use of the Herbicide Flumioxazin on Cotton*; D284045; William T. Drew et al; 5/24/2004.

4. *FLUMIOXAZIN - Exposure/Risk Assessment for the Use of FLUMIOXAZIN On Alfalfa, Pome & Stone Fruit, and Strawberry*; D303155; Shih-Chi Wang; 3/15/2005.

5. *Flumioxazin. Tolerance Petitions Requesting Section 3 Registration for Food Use of the Herbicide Flumioxazin on Pome Fruit, Stone Fruit, and Strawberries. Summary of Analytical Chemistry and Residue Data*; D310408 and D313783; William T. Drew; 3/15/2006.

6. *Flumioxazin Acute and Chronic Dietary Exposure Assessments for Tolerances (Associated with Section 3 Registration) on Pome Fruit (Crop Group 11), Stone Fruit(Crop Group 12), and Strawberries*; D325418; William T. Drew; 3/15/2006.

APPENDICES

A-1.0 THROUGH A-4.0

(These appendices are not available.)

A-5.0 SUMMARY OF MAGNITUDE OF THE RESIDUE STUDIES

APPENDIX TABLE 5 Summary of Residue Data from Strawberry, Pome Fruit, Stone Fruit, and Alfalfa Field Trials with Flumioxazin.

Commodity	Total Application Rate (lb ai/A)	PHI (Days)	Residue Levels (ppm)[1]					
			n	Min.	Max.	HAFT[2]	Mean	Std. Dev.
Strawberry (1 or 2 applications at 0.096 lb ai/A, 1-day PHI)								
Strawberry[3]	0.094-0.096	1-2	10	<0.020	0.050	0.043	0.022	0.016
	0.190-0.194	1	6	<0.020	0.034	0.028	0.016	0.010
Pome Fruit (2 applications at 0.3825 lb ai/A, 60-day PHI)								
Apple	0.76-0.79	56-61	24	<0.020	<0.020	<0.020	<0.020	0
Pear	0.76-0.78	59-61	12	<0.020	<0.020	<0.020	<0.020	0
Stone Fruit (2 applications at 0.3825 lb ai/A, 60-day PHI)								
Peach	0.76-0.79	53-60	18	<0.020	<0.020	<0.020	<0.020	0
Plum	0.74-0.78	59-60	12	<0.020	<0.020	<0.020	<0.020	0
Cherry	0.75-0.78	59-61	12	<0.020	<0.020	<0.020	<0.020	0
Alfalfa (1 application at 0.125 lb ai/A, 25-day PHI)								
Forage[4]	0.25	24-25	10	0.03	0.16	0.12	0.10	0.05
Hay[4]	0.25	24-25 + 3-8	10	0.06	0.36	0.35	0.22	0.13

1. The LOQ is 0.020 ppm for all fruit; the LOD is 0.004 ppm for strawberry, 0.010 ppm for stone and pome fruit.
2. HAFT = Highest Average Field Trial.
3. For calculation of the mean and standard deviation, ½LOQ was used for samples with residues less than the LOQ.
4. Field trials were conducted using 2 applications, but petitioner has revised proposed use to consist of only one application; therefore, alfalfa tolerances were set by entering the field trial dataset into the NAFTA Tolerance/MRL Harmonization spreadsheet, and then dividing the generated tolerances in half.

A-6.0 INTERNATIONAL CONSIDERATIONS

APPENDIX TABLE 6 International Residue Limit Status.			
Chemical Name: 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	**Common Name:** Flumioxazin	***X Proposed Tolerances*** 9 Reevaluated tolerance 9 Other	**Date:** 1/6/2006
Codex Status (Maximum Residue Limits)		**US Tolerances (Recommended)**	
X No Codex proposal step 6 or above 9 No Codex proposal step 6 or above for the crops requested		**Petition Number:** 4F6829, 4E6845, 04AZ02 **DP Number:** D325360 **Other Identifier:** PC Code 129034	
Residue definition (step 8/CXL): Flumioxazin		**Reviewer (Branch):** *William T. Drew (RAB2)*	
		Residue Definition: Flumioxazin	
Crop(s)	MRL (mg/kg)	**Crops**	**Tolerance (ppm)**
		Pome Fruit (Crop Group 11)	0.02
		Stone Fruit (Crop Group 12)	0.02
		Strawberry	0.07
		Alfalfa Forage	0.13
		Alfalfa Hay	0.45
Limits for Canada		Limits for Mexico	
X No Limits 9 No Limits for the crops requested		X No Limits 9 No Limits for the crops requested	
Residue definition: NA		Residue definition: NA	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
NOTES: per Stephen Funk, 1/6/2006. NA = Not Applicable.			

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R131969

Chemical: **Flumioxazin**

PC Code:
129034
HED File Code: **14000 Risk Reviews**
Memo Date: **3/15/2006**
File ID: ***00000000***
Accession #: **000-00-0108**

HED Records Reference Center
8/24/2006