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OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 10-NOV-2009

SUBJECT: Fludioxonil. New Use on Ornamentals. Human-Health Risk Assessment.

PC Code: 071503
Decision No.: 400716
Petition No.: None
Risk Assessment Type: Single chemical Aggregate
TXR No.: None
MRID No.: None

DP Barcode: D362493
Registration No.: 100-RGEI
Regulatory Action: Amended Section 3
Case No.: None
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HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational/residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the registered and proposed uses of fludioxonil (4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile) formulated as Palladium Fungicide (EPA Reg. No. 100-RGEI), a water-dispersible granule formulation containing 37.5% cyprodinil and 25% fludioxonil to ornamental crops. The registrant, Syngenta, has requested additional uses on ornamentals.

The risk assessment and dietary exposure assessments were prepared by William Wassell, the hazard assessment by Anwar Dunbar, the occupational/residential exposure assessment by Kelly Lowe, and the drinking water assessment by Chuck Peck of the Environmental Fate and Effects Division (EFED).

NOTE: In 2008, Alternative Risk Integration and Assessment Team (ARIA) of RD completed a Section 3 risk assessment for the application of fludioxonil to avocado, carrot, cucurbit, lemon, parsley, radish, sweet potato, tomato, and *Brassica* vegetables (Memo, 7/10/2008, B. Hanson, *et al.*, D342827). The current document contains only those aspects of the risk assessment which are affected by the addition of the proposed fludioxonil uses.

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1.0 EXECUTIVE SUMMARY

Fludioxonil is a contact fungicide and is active through inhibition of protein kinase leading to reduced growth and development. The registrant, Syngenta, has proposed foliar application of Palladium WDG (EPA Reg. No. 100-RGEI), a water dispersible granule formulation containing 37.5% cyprodinil and 25% fludioxonil to ornamental crops.

Fludioxonil is registered for foliar application (grape, strawberry, green onion, dry bulb onion, bushberry, caneberry, juneberry, lingonberry, pistachio, salal, and watercress), post-harvest application (stone fruit), and for seed treatment purposes (numerous crops) with tolerances for residues of fludioxonil ranging from 0.01 to 500 ppm (40 CFR 180.516(a)). A Section 18 registration is also established for post-harvest application to starfruit with a tolerance for residues of fludioxonil at 10 ppm (40 CFR 180.516(b)). Currently, there are no tolerances established for residues of fludioxonil in/on livestock commodities. Fludioxonil is also currently registered for use on residential turf and ornamentals.

Toxicology/Hazard

Fludioxonil is of low acute toxicity, since technical grade fludioxonil is in Toxicity Category III or IV for the full battery of acute tests and is not a dermal sensitizer. For subchronic and chronic toxicity, the primary effects in the mouse and rat were similar and included decreased body weight and food consumption associated with clinical pathological and histopathological effects in the liver and kidney. In the subchronic dog study, diarrhea was the most sensitive indicator of toxicity. In contrast, decreased weight gain in females was the most sensitive indicator of toxicity in the chronic toxicity study in dogs. Liver toxicity was observed in both dog studies at higher doses. The available data did not indicate a need for acute or subchronic neurotoxicity studies. Fludioxonil was not teratogenic in rabbits. In a rat developmental toxicity study, fludioxonil caused an increase in fetal incidence and litter incidence of dilated renal pelvis at the limit dose (1000 mg/kg/day). There was no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure to rats and rabbits or following pre-/postnatal exposure to rats.

Fludioxonil is classified as a Group D chemical - not classifiable as to human carcinogenicity; therefore, there is no need for a quantitative risk assessment. Fludioxonil was not mutagenic in the tests for gene mutations. However, based on the induction of polyploidy in the *in vitro* Chinese hamster ovary cell cytogenetic assay and the suggestive evidence of micronuclei induction in rat hepatocytes *in vivo*, additional mutagenicity testing was performed in three studies specifically designed to address the concerns regarding aneuploidy. The results of these assays were negative for aneuploidy activity.

In a 28-day dermal toxicity study in rats, the no-observed adverse-effect level (NOAEL) was equal to or greater than 1000 mg/kg/day (highest-dose tested (HDT)) based on no significant adverse effects in either sex.

In a rat metabolism study, tissue distribution showed that terminal residues were below the limit of detection (LOD) for most tissues except the liver, kidneys, blood, and lungs. The major route of excretion was the feces, with approximately 80% of the administered radioactivity excreted by this route in male and female rats at both the low and high dose. The remaining radioactivity was excreted through urine. In bile duct-cannulated rats, approximately 70% of an administered radioactive dose was excreted via this route, supporting the bile as the origin of the fecal radioactivity. There were no apparent sex or dose related differences in the routes of excretion for fludioxonil. Examination of urine for metabolites of fludioxonil showed at least 20 metabolites, each comprising a minor fraction of the administered dose (0.1 to 3.1%). There were no significant differences in urinary metabolites with sex or dose.

The toxicology database is essentially complete and there is no evidence of neurotoxicity or immunotoxicity in the hazard database for fludioxonil. While the new Part 158 requirements for an immunotoxicity study and acute and subchronic neurotoxicity studies have not yet been fulfilled for fludioxonil, the existing data are sufficient for endpoint selection for exposure/risk assessment scenarios and for evaluation of the requirements under the Food Quality Protection Act (FQPA). The acute toxicity and toxicological points of departure (PODs) for dietary, occupational/residential exposure and risk assessment for fludioxonil are summarized in Tables 1.1 and 1.2, respectively. The potential enhanced sensitivity of infants and children from exposure to fludioxonil, as required by the FQPA of 1996, was previously addressed by HED's FQPA Safety Factor Committee (6/13/2002), which concluded that the 10x safety factor should be reduced to 1x.

Table 1.1. Summary of Toxicological Endpoints for Use in Human-Health Dietary Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA Safety Factor	Study and Toxicological Effects
Acute Dietary (females 13-49 only)	NOAEL= 100 UF = 100 **Acute RfD** = 1.0 mg/kg/day	FQPA SF = 1x aPAD = acute RfD / FQPA SF = 1.0 mg/kg/day	The increased incidence of fetuses and litters with dilated renal pelvis and dilated ureter in rat developmental study.
Acute Dietary (general population including infants and children)	There were no appropriate toxicological effects attributable to a single exposure (dose) observed in available oral toxicity studies, including maternal toxicity in the developmental toxicity studies. Therefore, a dose and endpoint were not identified for this risk assessment.		
Chronic Dietary (all populations)	NOAEL = 3.3 UF = 100 **Chronic RfD** = 0.03 mg/kg/day	FQPA SF = 1x cPAD = chronic RfD / FQPA SF = 0.03 mg/kg/day	Decreased weight gain in female dogs during weeks 1-52 of one-year dog feeding study.
Cancer (oral, dermal, inhalation)	HED's Cancer Peer Review Committee has classified fludioxonil as a Group D chemical - not classifiable as to human carcinogenicity.		

[1] UF = uncertainty factor; NOAEL = no-observed adverse effect level; PAD = population-adjusted dose (a = acute, c = chronic); RfD = reference dose.

Table 1.2. Summary of Toxicological Endpoints for Use in Occupational and Non-Occupational Human-Health Risk Assessments.

Exposure Scenario	Dose Used in Risk Assessment, UF	Toxicological Effects	Study
Incidental Oral, Short-Term	NOAEL = 10 UF = 100	Decreased weight gain during dosing period.	Rabbit developmental study
Incidental Oral, Intermediate-Term	NOAEL = 3.3 UF = 100	Decreased weight gain in female dogs during weeks 1-13 of study.	One-year dog feeding study
Dermal, Short-and Intermediate-Term	No hazard identified and therefore quantification is not required. There are no developmental concerns via the dermal route and no systemic toxicity was seen following dermal exposure.		
Dermal, Long-Term	Oral NOAEL = 3.3 mg/kg/day* UF = 100	Decreased weight gain in female dogs during weeks 1-52 of study.	One-year dog feeding study
Inhalation, Short-Term	Oral NOAEL = 10 mg/kg/day** UF = 100	Decreased weight gain during dosing period.	Rabbit developmental study
Inhalation, Intermediate-Term	Oral NOAEL = 3.3 mg/kg/day** UF = 100	Decreased weight gain in female dogs during weeks 1-13.	One-year dog feeding study
Inhalation, Long-Term	Oral NOAEL = 3.3 mg/kg/day** UF = 100	Decreased weight gain in female dogs during weeks 1-52 of study.	One-year dog feeding study

* Dermal penetration of 40% is used with oral toxicity endpoint for route-to-route extrapolation.
** Inhalation absorption default value of 100% is used with oral toxicity endpoint for route-to-route extrapolation.

For aggregation of short- and intermediate-term risks, oral and inhalation exposures can be combined, since the PODs are based on a common endpoint. Dermal exposure cannot be combined with oral and inhalation, since a POD was not identified for short- and intermediate-term dermal exposure risk assessments. For long-term risk assessments, oral, dermal, and inhalation exposures can be combined, since each route of exposure is based on common target organs (oral equivalents).

Dietary Exposure (Food Plus Water)

No additional tolerances for residues of fludioxonil are requested as part of this action; however, the estimated drinking water concentrations (EDWCs) have increased. EDWCs are based on the highest application rate of 4 lbs ai/acre for the currently registered use on container-grown ornamentals.

Water Exposure and Risk

EDWCs were generated using EFED's standard suite of models. The Pesticide Root Zone Model (PRZM, v3.12.2, May 2005) and Exposure Analysis Modeling System (EXAMS, v2.98.4.6, April 2005) are simulation models used to generate EDWCs of fludioxonil residues that may occur in surface water used as drinking water. The PRZM model simulates pesticide movement and transformation on and across the agricultural field resulting from crop applications. Percent-cropped areas (PCA) that account for the maximum area within a watershed that may be planted with the modeled crop are applied to concentrations predicted by PRZM/EXAMS.

Screening Concentration in Ground Water (SCI-GROW v2.3, Jul. 29, 2003) is a regression model used as a screening tool to estimate pesticide concentrations found in ground water used as drinking water. The output of SCI-GROW represents the concentrations of fludioxonil that might be expected in shallow unconfined aquifers under sandy soils, which is representative of the ground water most vulnerable to pesticide contamination and likely to serve as a drinking water source.

Both models were run using the following application scenario: one application at a rate of 4.0 lbs ai/A. This application scenario is based on the currently registered container-grown ornamental use (Medallion® (EPA Reg. No. 100-769)) and provides the most conservative EDWCs for fludioxonil. The resulting acute and chronic EDWCs in surface water were 0.108 ppm (1-in-10-year acute estimate) and 0.053 ppm (1-in-10-year chronic estimate), respectively. The EDWCs for ground water for both acute and chronic analysis is 0.4 ppb. Since the surface water concentrations were the highest, the acute and chronic dietary runs were conducted assuming water residues of 0.108 ppm and 0.053 ppm, respectively, for all water sources (direct and indirect).

Acute and Chronic Dietary Exposure Results and Characterization

Acute and chronic dietary (food plus water) risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. This analysis was performed to support an additional use on ornamentals.

The acute analyses incorporated tolerance-level residues, 100% crop treated (CT), and DEEM (ver. 7.81) default processing factors. The 1-in-10-year acute drinking water estimate (i.e., relevant to acute exposure) of 0.108 ppm, provided by EFED, was directly incorporated into the acute assessment. This analysis was performed for the population subgroup females 13 to 49 years old, which is the only subgroup of interest for acute exposure. The acute dietary (food plus water) exposure utilizes 14% of acute population-adjusted dose (aPAD) for females 13 to 49 years old.

A chronic dietary assessment was performed assuming tolerance-level residues for most commodities with the exception of apple, grapefruit, lemon, lime, orange, and pear, 100% CT estimates, and DEEM (ver. 7.81) default processing factors with the exception of citrus fruit juice (1x), apple juice (1x), and tomato commodities (1x). These processing factors are based upon processing study data. Anticipated residue estimates (ARs) for apple, grapefruit, lemon, lime, orange, and pear were generated from field trial and processing study data for the chronic analysis. The 1-in-10-year chronic drinking water estimate (i.e., relevant to chronic exposure) of 0.053 ppm, provided by EFED, was directly incorporated into the chronic assessment. For the U.S. population, the dietary exposure (food plus water) utilized 49% of the chronic PAD (cPAD). The chronic dietary risk estimate for the highest reported exposed population subgroup, children 1 to 2 years old, is 90% of the cPAD. Based on a critical-commodity analysis conducted in DEEM-FCID, the major contributors to the chronic risk for children 1 to 2 years old were grape juice, head lettuce, orange juice, pome fruits, and peaches.

Fludioxonil is classified as a Group D chemical - not classifiable as to human carcinogenicity; therefore, there is no need for a quantitative risk assessment.

Non-Occupational and Residential Exposure/Risks

The current proposed label, Palladium, may be applied by homeowners. They are anticipated to have short-term dermal and inhalation exposure. However, since no short-term dermal POD was selected, only residential handler inhalation exposures are included in this document. The results of the residential handler exposure and risk assessment indicate that inhalation risks do not exceed the level of concern (i.e., margins of exposure (MOEs) greater than 100) for any of the ornamental scenarios. Post-application exposure following use of Palladium is possible; however, HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Therefore, post-application inhalation exposures and risks were not quantitatively assessed for the proposed uses in residential settings. Since no short-term dermal POD was selected, post-application dermal exposures and risks were not quantitatively assessed for the proposed uses on ornamentals in residential settings.

HED previously assessed the use of fludioxonil on residential turfgrass and ornamentals in residential settings (Memo, 5/6/2002, T. Swackhammer, D282570). Since the product registered for these residential uses, Medallion (EPA Reg. No. 100-769), is restricted to application by commercial applicators only, and since HED did not select short- or intermediate-term dermal PODs, only a toddler post-application assessment for incidental oral ingestion exposure to treated lawns was included. The MOEs for combined non-dietary oral exposures (hand-to-mouth, object-to-mouth and soil ingestion) were greater than 250 for short-term exposures. All intermediate-term aggregate risk estimates result in MOEs greater than 100, with the exception that the MOE for children 1-2 years old is just below 100.

Aggregate Exposure/Risks

Acute Aggregate Exposure

Acute aggregate risk estimates do not exceed the level of concern. Since the acute aggregate risk assessment includes only food and water, and the acute dietary analysis included both, no further calculations are necessary. Since the acute dietary risk does not exceed the level of concern, the acute aggregate risk does not exceed the level of concern.

Short-term Aggregate Exposure (Food + Water + Residential)

There is potential for short-term post-application exposure from commercial application of fludioxonil on residential turf (currently registered use), as well as residential handler exposure from application of fludioxonil to ornamentals (proposed use). Since no dermal POD was selected, the short-term aggregate assessment for toddlers includes exposure from food, water, and post-application non-dietary oral exposures (resulting from contact with treated lawns). For adults, short-term aggregate combines dietary (food + water) exposure with inhalation exposure (resulting from residential handlers treating ornamentals plants). The estimated MOEs range from 250 to 720, exceeding the target MOE of 100. Therefore, the short-term aggregate exposure and risk does not exceed the level of concern.

Intermediate-term Aggregate Exposure (Food + Water + Residential)

There is potential for intermediate-term post-application exposure from commercial application of fludioxonil on residential turf (currently registered use). Since no dermal PODs were selected, only non-dietary oral post-application exposures for toddlers on treated lawns were included in the intermediate-term aggregate risk assessment. The estimated MOEs exceed the target MOE of 100, with the exception of the MOE for children 1-2 years old is just below 100. Due to the conservative nature of the dietary (assumes 100% CT and tolerance-level residues for most commodities) and residential assessments (assumed that a toddler would be exposed to day-0 residues (no dissipation) daily for a period of up to 6 months), HED does not have concerns for this exposure scenario. Therefore, the intermediate-term aggregate risk and exposure does not exceed the level of concern.

Chronic Aggregate Exposure

Chronic aggregate risk estimates do not exceed the level of concern. Since no chronic residential exposure is expected to result from the residential uses of fludioxonil, the chronic aggregate risk assessment includes only food and water. As the chronic dietary analysis included both food and water, further estimates of risk are not necessary.

Occupational Exposure/Risks

No chemical-specific handler exposure data were submitted in support of this registration. It is the policy of HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure (ExpoSAC) Standard Operating Procedure (SOP) No. 7, dated 1/28/99) and to use data from the Outdoor Residential Exposure Task Force (ORETF), as applicable.

Occupational handlers are anticipated to have short- and intermediate-term dermal and inhalation exposures. However, since no short- or intermediate-term dermal PODs were selected, only inhalation exposures are assessed in this document. The results of the occupational handler exposure and risk assessment indicate that inhalation risks do not exceed the level of concern (i.e., MOEs greater than 100) at baseline level of risk mitigation (i.e., no respirator) for any of the ornamental handler scenarios.

Environmental Justice Consideration

Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under CSFII and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix C) have been determined to require a review of their ethical conduct, and have received that review.

Additional Data Needs

There are no outstanding occupational exposure data needs for fludioxonil.

Toxicology Deficiencies

Revised Part 158 requires that an immunotoxicity study and acute and subchronic neurotoxicity studies be submitted.

Recommendations for Use

HED has no objections to a conditional registration of fludioxonil on ornamentals as proposed in the subject request pending submission of an immunotoxicity study and acute and subchronic neurotoxicity studies.

2.0 INGREDIENT PROFILE

Summary of Proposed Use

Palladium fungicide is proposed for use to control diseases on ornamentals in production operations such as nurseries, greenhouses, and forest nurseries. It is also proposed for use on ornamentals and landscaped areas around residential, institutional, commercial and industrial buildings, parks, recreational areas, golf courses, and athletic fields. The maximum proposed application rate is 0.1875 lb ai/acre or 0.00094 lb ai/gallon for application to ornamentals.

3.0 HAZARD CHARACTERIZATION

NOTE: In 2008, ARIA of RD completed a Section 3 risk assessment for the application of fludioxonil to avocado, carrot, cucurbit, lemon, parsley, radish, sweet potato, tomato, and *Brassica* vegetables (Memo, 7/10/2008, B. Hanson, *et al.;* D342827). A complete discussion of the Hazard Assessment can be found in this previous risk assessment for fludioxonil.

Fludioxonil is of low acute toxicity, since technical grade fludioxonil is in Toxicity Category III or IV for the full battery of acute tests and is not a dermal sensitizer. For subchronic and chronic toxicity, the primary effects in the mouse and rat were similar and included decreased body weight and food consumption associated with clinical pathological and histopathological effects in the liver and kidney. In the subchronic dog study, diarrhea was the most sensitive indicator of toxicity. In contrast, decreased weight gain in females was the most sensitive indicator of toxicity in the chronic toxicity study in dogs. Liver toxicity was observed in both dog studies at higher doses. The available data did not indicate a need for acute or subchronic neurotoxicity studies. Fludioxonil was not teratogenic in rabbits. In a rat developmental toxicity study, fludioxonil caused an increase in fetal incidence and litter incidence of dilated renal pelvis at the limit dose (1000 mg/kg/day). There was no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure to rats and rabbits or following pre-/postnatal exposure to rats.

HED classified fludioxonil as a Group D chemical- not classifiable as to human carcinogenicity. There was no evidence of carcinogenicity in male or female CD-1 mice and male Sprague-Dawley rats following dietary administration at doses that were adequate for assessing the carcinogenic potential of fludioxonil. In female Sprague-Dawley rats, there was a statistically significant increase only when hepatocellular adenomas and carcinomas were combined (not for individual tumor types). Based on these findings and in accordance with the Agency's 1986 "Guidelines for Carcinogen Risk Assessment," fludioxonil was classified as a Group D Carcinogen; therefore, there is no need for a quantitative risk assessment. The cancer classification of fludioxonil was not re-assessed since no new information on carcinogenicity of the compound was required. The classification is based on the guidance used when this assessment was completed (1996) and should continue to be considered scientifically sound.

Fludioxonil was not mutagenic in the tests for gene mutations. However, based on the induction of polyploidy in the *in vitro* Chinese hamster ovary cell cytogenetic assay and the suggestive evidence of micronuclei induction in rat hepatocytes *in vivo*, additional mutagenicity testing was performed in three studies specifically designed to address the concerns regarding aneuploidy. The results of these assays were negative for aneuploidy activity.

In a 28-day dermal toxicity study in rats, the NOAEL was equal to or greater than 1000 mg/kg/day (HDT) based on no significant adverse effects in either sex.

In a rat metabolism study, tissue distribution showed that terminal residues were below the LOD for most tissues except the liver, kidneys, blood, and lungs. The major route of excretion was the feces, with approximately 80% of the administered radioactivity excreted by this route in male and female rats at both the low and high dose. The remaining radioactivity was excreted through urine. In bile duct-cannulated rats, approximately 70% of an administered radioactive dose was excreted via this route, supporting the bile as the origin of the fecal radioactivity. There were no apparent sex or dose related differences in the routes of excretion for fludioxonil. Examination of urine for metabolites of fludioxonil showed at least 20 metabolites, each comprising a minor fraction of the administered dose (0.1 to 3.1%). There were no significant differences in urinary metabolites with sex or dose.

3.1 FQPA Considerations

3.2 FQPA Safety Factor for Infants and Children

The fludioxonil risk assessment team recommends that the FQPA SF be reduced to 1x. This recommendation is based on the following considerations:

- There are no residual uncertainties in the toxicity database.
- There is no evidence of targeted neurotoxicity in the toxicity database, thus a developmental-neurotoxicity study (DNT) study is not required. There were no central nervous system (CNS) malformations present in the developmental toxicity studies in rats and rabbits. In a 2-generation study in rats, there were no findings in pups that were suggestive of changes in neurological development. Additionally, there was no evidence

of neurotoxicity in other studies. Therefore, it was determined that a DNT study was not required.

- There was no evidence of increased susceptibility following *in utero* exposure to rats and rabbits or following pre-/post-natal exposure to rats. In rats, developmental effects occurred in the presence of maternal effects. In rabbits, no developmental toxicity was seen up to the highest dose tested which demonstrated maternal toxicity. In the 2-generation rat reproduction study, offspring toxicity was seen at the dose that produced parental toxicity.
- The toxicology database for fludioxonil does not show any evidence of treatment-related effects on the immune or nervous system. The overall weight of evidence suggests that this chemical does not directly target these systems. In addition, fludioxonil does not belong to a class of chemicals (e.g., the organotins, heavy metals, halogenated aromatic hydrocarbons) that would be expected to be immunotoxic. Although immunotoxicity and acute and subchronic neurotoxicity studies are now required as a part of new data requirements in the 40CFR §158 for conventional pesticide registration, the Agency does not believe that conducting these studies will result in a lower POD than that currently use for overall risk assessment, and therefore, a database uncertainty factor (UF_{DB}) is not needed to account for lack of these studies.
- The dietary and residential exposure assessments do not underestimate exposure.

Table 3.2.1. Summary of Toxicological Endpoints for Use in Human-Health Dietary Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA Safety Factor	Study and Toxicological Effects
Acute Dietary (females 13-49 only)	NOAEL= 100 UF = 100 **Acute RfD** = 1.0 mg/kg/day	FQPA SF = 1x aPAD = acute RfD / FQPA SF = 1.0 mg/kg/day	The increased incidence of fetuses and litters with dilated renal pelvis and dilated ureter in rat developmental study.
Acute Dietary (general population including infants and children)	There were no appropriate toxicological effects attributable to a single exposure (dose) observed in available oral toxicity studies, including maternal toxicity in the developmental toxicity studies. Therefore, a dose and endpoint were not identified for this risk assessment.		
Chronic Dietary (all populations)	NOAEL = 3.3 UF = 100 **Chronic RfD** = 0.03 mg/kg/day	FQPA SF = 1x cPAD = chronic RfD / FQPA SF = 0.03 mg/kg/day	Decreased weight gain in female dogs during weeks 1-52 of one-year dog feeding study.
Cancer (oral, dermal, inhalation)	HED's Cancer Peer Review Committee has classified fludioxonil as a Group D chemical - not classifiable as to human carcinogenicity.		

[1] UF = uncertainty factor; NOAEL = no-observed adverse effect level; PAD = population-adjusted dose (a = acute, c = chronic); RfD = reference dose.

Table 3.2.2. Summary of Toxicological Endpoints for Use in Occupational and Non-Occupational Human-Health Risk Assessments.

Exposure Scenario	Dose Used in Risk Assessment, UF	Toxicological Effects	Study
Incidental Oral, Short-Term	NOAEL = 10 UF = 100	Decreased weight gain during dosing period.	Rabbit developmental study
Incidental Oral, Intermediate-Term	NOAEL = 3.3 UF = 100	Decreased weight gain in female dogs during weeks 1-13 of study.	One-year dog feeding study
Dermal, Short-and Intermediate-Term	No hazard identified and therefore quantification is not required. There are no developmental concerns via the dermal route and no systemic toxicity was seen following dermal exposure.		
Dermal, Long-Term	Oral NOAEL = 3.3 mg/kg/day* UF = 100	Decreased weight gain in female dogs during weeks 1-52 of study.	One-year dog feeding study
Inhalation, Short-Term	Oral NOAEL = 10 mg/kg/day** UF = 100	Decreased weight gain during dosing period.	Rabbit developmental study
Inhalation, Intermediate-Term	Oral NOAEL = 3.3 mg/kg/day** UF = 100	Decreased weight gain in female dogs during weeks 1-13.	One-year dog feeding study
Inhalation, Long-Term	Oral NOAEL = 3.3 mg/kg/day** UF = 100	Decreased weight gain in female dogs during weeks 1-52 of study.	One-year dog feeding study

* Dermal penetration of 40% is used with oral toxicity endpoint for route-to-route extrapolation.
** Inhalation absorption default value of 100% is used with oral toxicity endpoint for route-to-route extrapolation.

3.3 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) *"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."* Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, bifenazate may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

4.1. Drinking Water Residue Profile

EDWCs were generated using EFED's standard suite of models. The PRZM, v3.12.2, and EXAMS, v2.98.4.6, are simulation models used to generate EDWCs of fludioxonil residues that may occur in surface water used as drinking water. The PRZM model simulates pesticide movement and transformation on and across the agricultural field resulting from crop applications. PCA that account for the maximum area within a watershed that may be planted with the modeled crop are applied to concentrations predicted by PRZM/EXAMS.

SCI-GROW v2.3, is a regression model used as a screening tool to estimate pesticide concentrations found in ground water used as drinking water. The output of SCI-GROW represents the concentrations of fludioxonil that might be expected in shallow unconfined aquifers under sandy soils, which is representative of the ground water most vulnerable to pesticide contamination and likely to serve as a drinking water source.

Both models were run using the following application scenario: one application at a rate of 4.0 lbs ai/A. This application scenario is based on the currently registered container-grown ornamental use (Medallion® (EPA Reg. No. 100-769)) and provides the most conservative EDWCs for fludioxonil. The resulting acute and chronic EDWCs in surface water were 0.108 ppm (1-in-10-year acute estimate) and 0.053 ppm (1-in-10-year chronic estimate), respectively. The EDWCs for ground water for both acute and chronic analysis is 0.4 ppb. Since the surface water concentrations were the highest, the acute and chronic dietary runs were conducted assuming water residues of 0.108 ppm and 0.053 ppm, respectively, for all water sources (direct and indirect).

4.2 Dietary Exposure and Risk

Acute and chronic dietary (food plus water) risk assessments were conducted using the DEEM-FCID, Version 2.03, which uses food consumption data from the USDA's CSFII from 1994-1996 and 1998. This analysis was performed to support an additional use on ornamentals.

4.2.1 Acute Dietary Exposure/Risk

The acute analyses incorporated tolerance-level residues, 100% CT, and DEEM (ver. 7.81) default processing factors. The 1-in-10-year acute drinking water estimate (i.e., relevant to acute exposure) of 108 ppb, provided by EFED, was directly incorporated into the acute assessment. This analysis was performed for the population subgroup females 13 to 49 years old, which is the only subgroup of interest for acute exposure. The acute dietary (food plus water) exposure utilizes 14% of aPAD for females 13 to 49 years old.

There were no appropriate toxicological effects attributable to a single exposure (dose) for the general population or any other population subgroups; therefore these population subgroups were not included in this assessment.

4.2.2 Chronic Dietary Exposure/Risk

A chronic dietary assessment was performed assuming tolerance-level residues for most commodities with the exception of apple, grapefruit, lemon, lime, orange, and pear, 100% CT estimates, and DEEM (ver. 7.81) default processing factors with the exception of citrus fruit juice (1x), apple juice (1x), and tomato commodities (1x). These processing factors are based upon processing study data. ARs for apple, grapefruit, lemon, lime, orange, and pear were generated from field trial and processing study data for the chronic analysis. The 1-in-10 year chronic drinking water estimate (i.e., relevant to chronic exposure) of 53.0 ppb, provided by EFED, was directly incorporated into the chronic assessment. For the U.S. population the dietary exposure (food plus water) utilized 49% of the cPAD. The chronic dietary risk estimate for the highest reported exposed population subgroup, children 1 to 2 years old, is 90% of the cPAD. Based on a critical-commodity analysis conducted in DEEM-FCID, the major contributors to the chronic risk for children 1 to 2 years old were grape juice, head lettuce, orange juice, pome fruits, and peaches.

The results of the acute and chronic dietary exposure analyses are reported in the Summary Table (Table 4.2.2.1, below).

Table 4.2.2.1. Summary of Dietary Exposure (Food Plus Water) Assessment for Fludioxonil.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population			0.014707	49
All Infants (< 1 year old)			0.020766	69
Children 1-2 years old			**0.026946**	**90**
Children 3-5 years old			0.023268	78
Children 6-12 years old			0.016433	55
Youth 13-19 years old			0.011930	40
Adults 20-49 years old			0.013435	45
Adults 50+ years old			0.013896	46
Females 13-49 years old	**0.1389**	**14**	0.013903	46

* % PADs are reported to 2 significant figures. The values for the highest exposed population for each type of risk assessment are bolded.

4.2.3 Cancer Dietary Risk

Fludioxonil is classified as a Group D chemical - not classifiable as to human carcinogenicity; therefore, there is no need for a quantitative risk assessment.

4.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The chronic assessment was based on the assumption of tolerance-level residues for most commodities with existing and proposed tolerances and 100% CT. ARs for apple, grapefruit, lemon, lime, orange, and pear were previously generated from field trials, see Table 4.3, below.

ARs were determined for apple, grapefruit, lemon, lime and orange juices using average residues from field trials and processing factors from processing studies. Processing factors for tomato commodities were set to 1x based on processing data. DEEM-FCID default processing factors were used for all other processed commodities, as needed.

Table 4.3. Anticipated Residue Values Used for Apple, Grapefruit, Lemon, Lime, Orange and Pear Commodities

Commodity	Anticipated Residue (ppm)
Apple, whole	1.1
Juice	0.1
Grapefruit, whole	2.6
Juice	0.74
Lemon, whole	1.7
Juice	0.02
Lime, whole	1.7
Juice	0.02
Orange[1], whole	1.5
Juice	0.74
Pear, whole	1.6

[1] Also represents tangerine

Percent crop treated estimates were not use in the dietary assessment for fludioxonil.

5.0 RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK CHARACTERIZATION

For the proposed use, homeowners may experience post-application dermal and inhalation exposures to fludioxonil following the foliar use on ornamentals applied according to Palladium™ label specifications. HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since fludioxonil has low vapor pressure (2.9×10^{-9} mmHg), post-application inhalation exposures and risks were not quantitatively assessed. Further, since no short-term dermal PODs were selected, post-application dermal exposures and risks were not assessed.

In addition, HED previously assessed the use of fludioxonil on residential turfgrass and ornamentals in residential landscapes (Memo, 05/06/2002, T. Swackhammer, D282570). Since the product included in that assessment, Medallion (EPA Reg. No. 100-769), is restricted to application by commercial applicators only, and since HED did not select short- or intermediate-term dermal PODs, only a toddler post-application assessment for incidental oral ingestion exposures was included in this assessment. For a complete review of the potential risks and calculations associated with these residential uses of fludioxonil, please see the aforementioned memo (Memo, 05/06/2002, T. Swackhammer, D282570).

5.1 Residential Handler Risk

For the proposed use, residential handlers may experience short-term exposures to fludioxonil while performing foliar spray activities to ornamentals in residential settings. For all ornamental applications following Palladium label specifications, potential residential scenarios include:

- mixing/loading/applying sprays with low-pressure handwand sprayer,
- mixing/loading/applying sprays with backpack sprayer, and
- mixing/loading/applying sprays with hose-end sprayer.

Chemical-specific data for assessing exposure during pesticide handling activities (mixing/loading/applying) were not submitted in support of registration. It is HED policy to use data from PHED Version 1.1 and, if appropriate, the ORETF to assess residential handler exposures for regulatory actions when chemical-specific data are not available (HED ExpoSAC, SOP No. 7, January 1999). Unit exposure data were taken from ORETF for the low-pressure handwand and hose-end sprayer scenarios and from PHED for backpack sprayer applications. Residential handlers are assumed to be wearing short-sleeved shirts, short pants, shoes, and socks.

Based on HED ExpoSAC SOP No. 9.1, the amount handled in a day was assumed to be:

5 gallons for mixing/loading/applying with a low-pressure handwand sprayer,
- 5 gallons for mixing/loading/applying with backpack sprayer, and
- 100 gallons for mixing/loading/applying with a hose-end sprayer.

The average adult body weight of 70 kg was used for estimating inhalation dose, since the POD is not sex-specific. Since the short- and intermediate-term inhalation PODs are based on an oral study and no inhalation absorption data are available, estimated toxicity by the inhalation route is considered to be equivalent to the toxicity by the oral route of exposure.

Daily dermal or inhalation handler exposures are estimated for each applicable handler task with the application rate, the area treated in a day, and the applicable dermal or inhalation unit exposure using the following formula:

Daily Exposure (mg ai/day) = Unit Exposure (mg ai/lb ai handled) x Application Rate (lb ai/area) x Daily Area Treated (area/day)

Where:

Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Unit Exposure	=	Unit exposure value (mg ai/lb ai) derived from August 1998 PHED data or from ORETF data;

Application Rate	=	Normalized application rate based on a logical unit treatment, such as acres, square feet, or gallons. Maximum values are generally used (lb ai/A, lb ai/sq ft, lb ai/gal); and
Daily Area Treated	=	Normalized application area based on a logical unit treatment such as acres (A/day), square feet (sq ft/day), gallons per day (gal/day).

The daily dermal or inhalation dose is calculated by normalizing the daily exposure by body weight and adjusting, if necessary, with an appropriate dermal or inhalation absorption factor using the following formula:

Average Daily Dose (mg/kg/day) = Daily Exposure (mg ai/day) x (Absorption Factor (%/100) / Body Weight (kg)

Where:

Average Daily Dose	=	Absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day);
Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Absorption Factor	=	A measure of the amount of chemical that crosses a biological boundary such as the skin or lungs (% of the total available absorbed; 1% for fludioxonil); and
Body Weight	=	Body weight determined to represent the population of interest in a risk assessment (60 kg for fludioxonil).

Non-cancer dermal and inhalation risks for each applicable handler scenario are calculated using a MOE, which is a ratio of the NOAEL or LOAEL to the daily dose. In the case of fludioxonil, a NOAEL was used in the calculation. All MOE values were calculated using the formula below:

MOE = NOAEL (mg/kg/day) / Average Daily Dose (mg/kg/day)

A summary of the inhalation risks for each residential exposure scenario is presented in Table 5.1.1 for short-term inhalation exposure. The results of the short-term residential handler exposure and risk assessment indicate that inhalation risks do not exceed the level of concern (i.e., MOEs greater than 100) at baseline level of risk mitigation for any of the ornamental exposure scenarios on the Palladium label.

Table 5.1.1. Fludioxonil - Residential Handler Exposures and Risks

Exposure Scenario	Application Directed At	Application Rate[a] (lb ai/gallon)	Amt Handled Daily (gallons)	Inhalation Unit Exposure[b] (µg/lb ai)	Inhalation Dose[c] (mg/kg/day)	Inhalation MOE[d] (Target MOE = 100)
Mixing/Loading/Applying Dry Flowables with Low Pressure Handwand (using liquids as a surrogate; ORETF OMA005; MRID 445185-01)	overhead	0.00094 lb ai/gallon	5 gallons	3.8	2.6E-07	39,000,000
Mixing/Loading/Applying Dry Flowables with Low Pressure Handwand (using liquids as a surrogate; ORETF OMA006; MRID 444598-01)	ground		5 gallons	2.7	1.8E-07	55,000,000
Mixing/Loading/Applying Dry Flowables with a Backpack (using liquids as a surrogate; PHED)	NA		5 gallons	30	2.0E-06	5,000,000
Mixing/Loading/Applying Dry Flowables with Hose-End Sprayer (using liquids as a surrogate; ORETF OMA006; MRID 444598-01)	ground		100 gallons	0.82	1.1E-06	9,100,000
Mixing/Loading/Applying Dry Flowables with Hose-End Sprayer (using liquids as a surrogate; ORETF OMA005; MRID 445185-01)	overhead		100 gallons	1.5	2.0E-06	5,000,000

a. Application rates based on proposed ornamental uses on label for Palladium (EPA Reg. No. 100-RGEI).
b. Unit exposures from ORETF unless noted otherwise.
c. Inhalation dose (mg/kg/day) = daily unit exposure (µg/lb ai) x application rate (lb ai/gallon) x amount handled /day (gallons/day) x conversion factor (1 mg/1,000 µg) x absorption factor (100%) / body weight (70 kg adult).
d. Inhalation MOE = short-term inhalation NOAEL (10 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.

5.2 Residential Post-application Risk

As discussed previously, no quantitative assessment of post-application exposure was performed for the proposed use on ornamentals. For the previously assessed fludioxonil use on residential turfgrass and ornamentals in residential landscapes (Memo, 05/06/2002, T. Swackhammer, D282570), toddlers incidental oral ingestion exposures were assessed. None of the calculated MOEs exceed the HED's level of concern for residential exposures (MOEs < 100). It should be noted that risk estimates for intermediate-term exposures should be considered very conservative, since it was assumed that a toddler would be exposed to day 0 residues (no dissipation) daily for a period of up to 6 months. It should also be noted that each of the incidental oral assessments (i.e., hand-to-mouth, object-to-mouth and soil ingestion) are considered conservative. Therefore,

combining all the assessments is expected to provide a highly conservative assessment of children's incidental oral exposure.

Table 5.2.1. Summary of Toddler Incidental Oral Ingestion Exposures and Risk Estimates for Residential Use of Fludioxonil[1]

Activity	Application Rate (AR; lbs ai/A)[2]	Residue Estimate[3]	Potential Dose Rate (mg/kg bw/d)[4]	MOEs[5] (DAT 0)
Hand-to-mouth	0.68	DFR: 0.381 µg/cm^2	S/T: 0.0102 I/T: 0.00483	S/T: 980 I/T: 680
Object-to-mouth		DFR: 1.53 µg/cm^2	0.00255	S/T: 3,900 I/T: 1,300
Soil Ingestion		Soil residue: 5.11 µg/g soil	3.41 x 10^{-5}	S/T: 290,000 I/T: 97,000
Combined oral exposure	--	--	S/T: 0.0128 I/T: 0.00741	S/T: 770 I/T: 450

1. Sources: SOPs for Residential Exposure Assessments, Draft, December 17, 1997 and Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.
2. AR = maximum application rate on Medallion® label (EPA Reg. No. 100-769; ai = fludioxonil only) for residential lawn treatment for turfgrass disease control.
3. Residue estimates based on the following protocol from the Residential SOPs:
   a. Hand-to-mouth DFR = 0.68 lb ai/A x 0.05 x (4.54 x 108 µg/lb ai) x (2.47 x 10-8 A/cm2) = 0.381µg/cm2.
   b. Object-to-mouth DFR = 0.68 lb ai/A x 0.20 x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) = 1.53µg/cm^2.
   c. Soil Residue = 0.68 lb ai/A x fraction of residue in soil (100%)/cm x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) x 0.67 cm^3/g= 5.11 µg/g soil.
4. Potential Dose Rate (PDR; normalized to body weight of toddler).
   a. S/T Hand-to-mouth PDR = (0.381 µg/cm^2 x 0.50 x 20 cm^2/event x 20 events/hr x 10^{-3} mg/µg x 2 hrs/d)/15 kg = 0.0102 mg/kg bw/d; I/T Hand-to-mouth PDR = (0.381 µg/cm^2 x 0.50 x 20 cm^2/event x 9.5 events/hr x 10^{-3} mg/µg x 2 hrs/d)/15 kg = 0.00483 mg/kg bw/d.
   b. Object-to-mouth PDR = (1.53 µg/cm^2 x 25 cm^2/d x 10^{-3} mg/µg)/15 kg = 0.00255 mg/kg bw/d.
   c. Soil Ingestion PDR = (5.11 µg/g soil x 100 mg soil/d x 10^{-6} g/µg)/15 kg = 3.41 x 10^{-5} mg/kg bw/d.
5. MOE = NOAEL/PDR, where the short-term incidental oral NOAEL = 10 mg/kg bw/d; intermediate-term incidental oral NOAEL = 3.3 mg/kg bw/d; HED's level of concern is for MOEs < 100 (short-term residential).

For a complete review of the potential risks and calculations associated with these residential uses of fludioxonil, please see the aforementioned T. Swackhammer memo.

5.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but to a lesser extent, could also be a potential source of exposure from the ground application method employed for fludioxonil. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift

management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

6.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from non-occupational sources, including; food, drinking water, and residential pathways. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

6.1 Acute Aggregate Risk

Since the acute aggregate risk assessment includes exposure from food and water only, and the acute dietary analysis that was performed included both, no further estimates of risk are necessary. Since the acute dietary risk does not exceed the level of concern, the acute aggregate risk does not exceed the level of concern.

6.2 Short-Term Aggregate Risk

In aggregating short-term risk, HED considers background chronic dietary exposure (food + water) and short-term, residential exposures. The proposed label allows for residential handler application of fludioxonil to ornamentals; however, the previous assessment for fludioxonil for residential turfgrass and ornamentals specified that the residential application of fludioxonil was restricted to commercial handlers. Therefore, no residential handler exposure is expected from the currently registered use. Additionally, there is potential for post-application exposure resulting from the residential uses of fludioxonil. However, since no dermal POD was selected and post-application inhalation exposure is expected to be minimal, the only short-term residential exposures are (1) incidental oral post-application exposures for toddlers on treated lawns (resulting from the currently registered use) and (2) inhalation exposure for residential handlers (resulting from the proposed use). The short-term aggregate assessment for toddlers includes exposure from food, water, and post-application non-dietary oral exposures (resulting from contact with treated lawns). For adults, short-term aggregate combines dietary (food + water) exposure with inhalation exposure (resulting from residential handlers treating ornamentals plants).

Tables 6.2.1 and 6.2.2 summarize the short-term aggregate exposure estimates to fludioxonil residues.

Table 6.2.1. Short-Term Aggregate Risk (Food, Drinking Water and Residential Exposure).					
Population	Short-Term Scenario				
	NOAEL mg/kg/day	LOC MOE [1]	Average Food + Water Exposure mg/kg/day	Oral Residential Exposure[2] mg/kg/day	Aggregate MOE (food, water & residential)[3]
All Infants (< 1 year old)	10	100	0.020766	0.013	300
Children (1-2 years)	10	100	0.026946	0.013	250
Children (3-5 years)	10	100	0.023268	0.013	280

[1] The level of concern (LOC) MOE is 100, based on inter- and intra-species safety factors totaling 100.
[2] Oral residential exposure = [incidental oral exposure from all possible sources]. From Table 5.2.1.
[3] Aggregate MOE = [NOAEL ÷ (avg. food + water exposure + residential exposure)].

Table 6.2.2. Short-Term Aggregate Risk (Food, Drinking Water and Residential Exposure).					
Population	Short-Term Scenario				
	NOAEL mg/kg/day	LOC MOE[1]	Average Food + Water Exposure mg/kg/day	Inhalation Residential Exposure[2] mg/kg/day	Aggregate MOE (food, water & residential)[3]
U.S. Population	10	100	0.014707	2.0E-6	680
Females 13-49 Years	10	100	0.013903	2.0E-6	720

[1] The level of concern (LOC) MOE is 100, based on inter- and intra-species safety factors totaling 100.
[2] Inhalation exposure from Table 5.1.1.
[3] Aggregate MOE = [NOAEL ÷ (avg. food + water exposure + residential exposure)].

All short-term aggregate risk estimates result in MOEs greater than 100. Short-term aggregate exposure to fludioxonil, as a result of all registered and proposed uses, is below the level of concern.

6.3 Intermediate-Term Aggregate Risk

In aggregating intermediate-term risk, HED consider background chronic dietary exposure (food + water) and intermediate-term, residential non-dietary oral and dermal exposures. Based on the residential use pattern, there is a possibility, although unlikely, that a toddler may experience intermediate-term exposures to fludioxonil residues on treated lawns. As with the short-term aggregate assessment, only non-dietary exposures are included for toddlers. Intermediate-term exposure for residential handlers of the proposed ornamental product is not expected. Therefore, the intermediate-term aggregate risk for fludioxonil considers food, water, and residential non-dietary oral exposures (for toddlers).

Tables 6.3.1 and 6.3.2 summarize the intermediate-term aggregate exposure estimates to fludioxonil residues.

Table 6.3.1. Intermediate-Term Aggregate Risk (Food, Drinking Water and Residential Exposure)

Population	Intermediate-Term Scenario				
	NOAEL mg/kg/day	LOC MOE[1]	Average Food + Water Exposure mg/kg/day	Oral Residential Exposure[2] mg/kg/day	Aggregate MOE (food, water & residential)[3]
All Infants (< 1 year old)	3.3	100	0.020766	0.0074	120
Children (1-2 years)	3.3	100	0.026946	0.0074	96
Children (3-5 years)	3.3	100	0.023268	0.0074	108

[1] The level of concern (LOC) MOE is 100, based on inter- and intra-species safety factors totaling 100.
[2] Oral residential exposure = [incidental oral exposure from all possible sources]. From Table 5.2.1.
[3] Aggregate MOE = [NOAEL ÷ (avg. food + water exposure + residential exposure)].

All intermediate-term aggregate risk estimates result in MOEs greater than 100, with the exception of the MOE for children 1-2 years old which is just below 100. Due to the conservative nature of the dietary (assumes 100% CT) and residential assessments (assumed that a toddler would be exposed to day 0 residues (no dissipation) daily for a period of up to 6 months), HED does not have any concern for the purposes of this action. Intermediate-term aggregate exposures to fludioxonil, as a result of all registered and proposed uses, are below the level of concern.

6.4 Chronic Aggregate Risk

Since chronic residential exposure is not expected to result from the residential uses of fludioxonil, the chronic aggregate risk assessment includes exposures from food and water only. As the chronic dietary analysis that was performed included both food and water, no further calculations are necessary. Since the chronic dietary risk does not exceed the level of concern, the chronic aggregate risk does not exceed the level of concern.

6.5 Cancer Aggregate Risk

Fludioxonil has been classified as a Group D chemical – not classifiable as to human carcinogenicity; therefore, there is no need for a quantitative risk assessment.

7.0 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 fludioxonil and any other substances, and fludioxonil 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 fludioxonil 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 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/.

8.0 OCCUPATIONAL EXPOSURE/RISK PATHWAY

Fludioxonil can be used as a protectant fungicide for control of certain stem and root diseases of ornamental plantings in residential and commercial landscapes. Based on the proposed Palladium label for foliar use on ornamentals, occupational handler exposure is expected for individuals involved in mixing/loading, applying, and mixing/loading/applying the WDG formulation.

8.1 Occupational Handler Risk

Occupational handlers may experience short- and intermediate-term dermal exposure to fludioxonil while performing tasks involving applications to ornamentals in commercial and residential settings. However, since no short- or intermediate-term dermal PODs were selected, no occupational post-application dermal exposures and risks are assessed. Occupational handler short- and intermediate-term inhalation exposures are anticipated.

For applications to ornamentals following Palladium label specifications, potential occupational handler exposure scenarios include:

- mixing/loading WDG formulations for groundboom application;
- mixing/loading WDG formulation for lawn-care operator (LCO) hand-gun sprayer application;
- applying sprays with a groundboom sprayer;
- applying sprays with hand-gun sprayer;
- mixing/loading/applying liquid formulations with a low-pressure handwand sprayer;
- mixing/loading/applying liquid formulations with a backpack sprayer; and
- mixing/loading/applying liquid formulations with a high-pressure handwand sprayer.

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (August, 1998). No data are available to assess exposures using WDG formulations with low-pressure handwand sprayers, backpack sprayers, or high-pressure handwand sprayers; therefore, data for mixing/loading/applying liquid formulations is used as a reasonable surrogate.

For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" (i.e., workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, and no protective gloves), as well as for "baseline" and the use of protective gloves or other personal-protective equipment (PPE) as might be necessary. The Palladium product label involved in this assessment directs applicators and other handlers to wear a long-sleeved shirt and long pants; shoes plus socks; and chemical-resistant gloves.

Handler exposure is expected to be short- or intermediate-term based on information provided on proposed labels. In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term duration exposures. Long-term exposures are not expected, therefore, a long-term assessment was not conducted. The average adult body weight of 70 kg was used for estimating dermal and inhalation dose. Since the short- and intermediate-term inhalation PODs are based on an oral study and no inhalation absorption data are available, toxicity by the inhalation route is considered to be equivalent to the estimated toxicity by the oral route of exposure.

Based on HED ExpoSAC SOP No. 9.1, the area or amount handled in a day was assumed to be:

- 20 acres for mixing/loading to support groundboom applications;
- 1000 gallons for mixing/loading to support LCO handgun applications;
- 20 acres for applying sprays with groundboom equipment;
- 5 acres for LCO handgun applications;
- 40 gallons for mixing/loading/applying with a low-pressure handwand sprayer;
- 40 gallons for mixing/loading/applying with backpack sprayer; and
- 1000 gallons for mixing/loading/applying with a high-pressure handwand sprayer.

Daily dermal or inhalation handler exposures are estimated for each applicable handler task with the application rate, the area treated in a day, and the applicable dermal or inhalation unit exposure using the formula provided previously in the residential exposure section.

A summary of the inhalation risks for each exposure scenario is presented in Table 8.1.1 for short- and intermediate-term inhalation exposures to occupational handlers. The results of the short- and intermediate-term occupational handler exposure and risk assessment indicate that inhalation risks do not exceed the level of concern (i.e., MOEs greater than 100) at baseline level of risk mitigation (i.e., no respirator) for any of the ornamental exposure scenarios on the Palladium label.

Table 8.1.1. Fludioxonil – Occupational Exposures and Risks.

Exposure Scenario	Application Rate[a]	Area Treated Daily	Baseline Inhalation Unit Exposure[b] (ug/lb ai)	Baseline Inhalation Dose[c]	Baseline Inhalation MOEs[d] Target MOE = 100	
					Short-Term	Intermediate-Term
Mixing/Loading Dry Flowables for Groundboom Applications	0.1875 lb ai/acre	20 acres	0.77	4.1E-05	240,000	80,000
Mixing/Loading Dry Flowables to Support LCO Handgun Applications (mixing/loading supports 20 LCOs)	0.00094 lb ai/gallon	1000 gallons		1.0E-05	970,000	320,000
Applying Sprays via Groundboom Equipment	0.1875 lb ai/acre	20 acres	0.74	4.0 E-05	250,000	83,000
Applying Sprays via Handgun Equipment	0.00094 lb ai/gallon	5 acres	1.4	1.9E-05	530,000	180,000
Mixing/Loading/Applying Dry Flowables with Low-Pressure Handwand (using wettable powders as a surrogate; PHED)		40 gallons	1.1	5.9 E-04	17,000	56,000
Mixing/Loading/Applying Dry Flowables with a Backpack (using liquids as a surrogate; PHED)		40 gallons	30	1.6 E-05	620,000	200,000
Mixing/Loading/Applying Dry Flowables with a High-Pressure Handwand (using liquids as a surrogate; PHED)		1000 gallons	120	1.6 E-03	6,200	2,000

a. Application rates based on proposed ornamental use on label for Palladium (EPA Reg. No. 100-RGEI).
b. Unit exposures from PHED unless noted otherwise. Baseline inhalation unit exposure signifies no respirator use.
c. Inhalation dose (mg/kg/day) = daily unit exposure (µg/lb ai) x application rate (lb ai/acre or lb ai/gallon) x amount treated or handled /day (acres/day or gallons/day) x conversion factor (1 mg/1,000 µg) x absorption factor (100%) / body weight (70 kg adult).
d. Inhalation MOE = NOAEL (10 mg/kg/day for short-term exposure and 3.3 mg/kg/day for intermediate-term exposure) / inhalation daily dose (mg/kg/day). Level of concern = 100.

8.2 Occupational Post-Application Risk

Fludioxonil has low vapor pressure (2.9×10^{-9} mmHg). HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure; therefore, post-application inhalation exposures and risks were not quantitatively assessed. Since no short-term dermal POD was selected, no post-application dermal exposures and risks are assessed.

9.0 DATA NEEDS AND LABEL RECOMMENDATIONS

No additional occupational risk data are required.

Toxicology

- Revised Part 158 requires an immunoxicity, as well as acute and subchronic neurotoxicity studies to be submitted as well. The data requirements pertaining to immunotoxicity, acute and subchronic neurotoxicity must be fulfilled as a condition of registration.

Attachment A: Toxicology Profile Tables.

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Appendix A: Toxicity Profile

Acute Toxicity Profile.

Table 1. Acute Toxicity of Technical Grade Fludioxonil.				
Guideline No.	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute Oral	43124105	LD50 > 5000 mg/kg	IV
870.1200	Acute Dermal	43124106	LD50 > 2000 mg/kg	III
870.1300	Acute Inhalation	43080019	LC50 = 2.636 m/L	IV
870.2400	Primary Eye Irritation	43124107	slight irritant	III
870.2500	Primary Skin Irritation	43124108	non-irritating	IV
870.2600	Dermal Sensitization	43080024	not a sensitizer	-

Toxicity Profile of Fludioxonil.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100a 90-Day oral toxicity in rats	43080026 (1990) Acceptable/guideline 0, 10, 100, 1000, 7000, 20,000 ppm M: 0.8, 6.6, 64, 428, 1283 mg/kg/day F: 1.0, 7.1, 70, 462, 1288 mg/kg/day	NOAEL = 64 mg/kg/day (M) and 70 mg/kg/day (F). LOAEL = 428 mg/kg/day (M) and 462 mg/kg/day (F) based on decreased weight gain (both sexes), chronic nephropathy (M), and centrilobular hepatocyte hypertrophy (F).
870.3100b 90-Day oral toxicity in mice	43080027 (1990) Acceptable/guideline 0, 10, 100, 1000, 3000, 7000 ppm M:1.3, 13.9, 144, 445, 1052 mg/kg/day F: 1.9, 16.8, 178, 559, 1307 mg/kg/day	NOAEL = 445 mg/kg day (M) and 559 mg/kg/day (F). LOAEL = 1052 mg/kg/day (M) and 1307 mg/kg/day (F) based on decreased body weight gain (F), increased alkaline phosphatase (M), increased relative liver weight, increased incidence of nephropathy and centrilobular hypertrophy (both sexes).
870.3100c 90-Day oral toxicity in dogs	43080029 (1990) Acceptable/guideline 0, 200, 2000, 15,000/10,000 ppm M & F: 5, 50, 375/250 mg/kg/day	NOAEL = 5 mg/kg/day (both sexes). LOAEL = 50 mg/kg/day based on an increased incidence of diarrhea (both sexes).
870.3200 21/28-Day dermal toxicity in rats	43080030 (1990) Acceptable/guideline M & F: 0, 40, 200 or 1000 mg/kg/day	NOAEL ≥1000 mg/kg/day for both sexes.
870.3250 90-Day dermal toxicity in rats	NA	NA
870.3465 90-Day inhalation	NA	NA

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
toxicity in rats		
870.3700a Prenatal developmental toxicity in rats	43080034 (1988) Acceptable/guideline F: 0, 10, 100, or 1000 mg/kg/day	Maternal NOAEL = 100 mg/kg/day. LOAEL = 1000 mg/kg/day based on reduction in corrected weight gain. Developmental NOAEL = 100 mg/kg/day. LOAEL = 1000 mg/kg/day based on increase in the fetal incidence and litter incidence of dilated renal pelvis and dilated ureter.
870.3700b Prenatal developmental toxicity in rabbits	43080035 (1989) Acceptable/guideline F: 0, 10, 100, or 300 mg/kg/day	Maternal NOAEL = 10 mg/kg/day. LOAEL = 100 mg /kg/day based on decreased body weight gain and decreased food efficiency. Developmental NOAEL ≥300 mg/kg/day.
870.3800 Reproduction and fertility effects in rats	43080036 (1992) Acceptable/guideline 0, 30, 300, or 3,000 ppm F0F1 M: 2.19, 22.13, 221.61 mg/kg/day F0F1 F: 2.45, 24.24, 249.67 mg/kg/day	Parental/Systemic NOAEL = 22.13 mg/kg/day (M) and 24.24 mg/kg/day (F). LOAEL = 221.61mg/kg/day (M) and 249.67 mg/kg/day (F) based on increased clinical signs, decreased body weights, decreased weight gain, and decreased food consumption in both sexes Reproductive/Offspring NOAEL = 22.13 mg/kg/day (M) and 24.24 mg/kg/day (F). LOAEL = 221.61 mg/kg/day (M) and 249.67 mg/kg/day (F) based on reduced pup weights during lactation.
870.4100b Chronic toxicity in dogs	43080031 (1992) Acceptable/guideline 0, 100, 1000, or 8,000 ppm M: 0, 3.1, 33.1, or 297.8 mg/kg/day F: 0, 3.3, 35.5, or 330.7 mg/kg/day	NOAEL = 3.3 mg/kg/day (F) and 33.1 mg/kg/day (M). LOAEL = 35.5 mg/kg/day (F) and 297.8 mg/kg/day (M) based upon decreased weight gain (F) and decreased body weight, reduction in hematological parameters (platelets), increase in cholesterol and alkaline phosphatase, and increased relative liver weight (M).
870.4300 Combined Chronic Toxicity/Carcino-genicity in rats	43080037 (1993) Acceptable/guideline 0,10, 30, 100, 1,000, or 3,000 ppm M: 0.37, 1.1, 3.7, 37, or 113 mg/kg/day F: 0.44, 1.3, 4.4, 44, or 141 mg/kg/day	NOAEL = 37 mg/kg/day (M) and 44 mg/kg/day (F). LOAEL = 113 mg/kg/day (M) and 141 mg/kg/day (F) based on decreased mean body weight gain, slight anemia (F), and increased incidence and severity of liver lesions (degeneration) in both sexes. There was no evidence of carcinogenicity in male rats, but there was a statistically significant increase, both trend and pairwise, of combined hepatocellular tumors in female rats. Classified as a Group D chemical by HED Cancer Peer Review Committee.
870.4200a Carcinogenicity in Mice	43080032 (1993) 0, 10, 100, 1,000 or 3,000 ppm M: 1.1, 11.3, 112, or 360 mg/kg/day F: 1.4, 13.5, 133, or 417 mg/kg/day	NOAEL = 11.3 mg/kg/day (M) and 133 mg/kg/day (F). LOAEL = 112 mg/kg/day (M) and 417 mg/kg/day (F) based on the increased incidence of mice convulsing when handled (M) and increased absolute liver weight and grossly enlarged livers (F). Statistically significant trend for malignant lymphomas in females.
870.4200b Carcinogenicity in mice	43080033 (1993) Acceptable/guideline 0, 3, 30, 5000, or 7,000 ppm M: 0.33, 3.3, 590, or 851 mg/kg/day F: 0.41, 4.1, 715, or 1,008 mg/kg/day	NOAEL = 590 mg/kg/day (M) and 715 mg/kg/day (F). LOAEL: 851 mg/kg/day (M) and 1,008 mg/kg/day (F) based on reduced survival (F), decreased body weights (M), bile duct hyperplasia (M) and severe nephropathy (both sexes). No evidence of carcinogenicity.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5100 Gene mutation in bacteria	43080038 (1989) Acceptable/guideline	Strains TA 98, 100, 1535, 1537 of *S. typhimurium*, and strain WP2uvrA of E. coli were negative for mutagenic activity when tested from 20 to 5000 µg/plate in absence and presence of metabolic activation.
870.5300 Gene mutation in mammalian cells in culture	43152501 (1989) Acceptable/guideline	Chinese hamster V79 ovary cells were tested from 0.50 to 60 µg/mL. Negative up to limit of solubility and cytotoxicity.
870.5375 *in vitro* Chromosome aberration	43080040 (1989) Acceptable/guideline	Chinese hamster ovary cells were tested with and without metabolic activation from 1.37 to 700 µg/mL. Positive for nondisjunction of chromosomes both in the presence and absence of activation.
870.5385, bone marrow chromosome aberrations assay	43080042 (1993) Acceptable/guideline	Chinese hamsters were orally dosed at levels from 1250 to 5,000 mg/kg. There was no significant increase in the frequency of chromosome aberrations in bone marrow at any dose tested.
870.5395 In vivo Mouse micronucleus assay	43080041 (1990) Acceptable/guideline	Both sexes of NMRI mice were dosed up to 5,000 mg/kg/day. There were no significant increases in the number or percentage of micronucleated polychromatic erythrocytes.
870.5395 In vivo Rat hepatocyte micronucleus assay	43080043 (1991) Acceptable/guideline	Male rats were orally dosed 1250, 2500 and 5000 mg/kg and hepatocytes were harvested. Micronucleated hepatocytes were found in Phase II at the low and mid dose levels but not at the high dose level and not in Phase I. Positive for mutagenicity in hepatocytes exposed *in vivo*.
870.5550 in vitro unscheduled DNA synthesis assay	43080039 (1989) Acceptable/guideline	There was no evidence of unscheduled DNA synthesis in rat hepatocytes at doses from 4.1 to 5000 µg/mL.
870.5450 dominant lethal assay in mice	43080044 (1992) Acceptable/guideline	Male mice singly dosed at 0, 1250, 2500, or 5000 mg/kg/day and mated for 8 consecutive weeks had no evidence of a dominant lethal mutation.
870.7485 Metabolism in rats	43560504, 43560505, 43429513 (1990) Acceptable/ guideline	C14-Fludioxonil given by gavage and bile duct-cannulation to groups of male and female rats. Absorption was estimated to be between 67-91%. Terminal tissue distribution showed that terminal residues were below the limit of detection for most tissues except the liver, kidneys, blood, and lungs, which showed low levels. The major route of excretion was the feces, with approximately 80% of the administered radioactivity excreted by this route in male and female rats at both the low and high dose. The remaining radioactivity was excreted through urine. In bile duct-cannulated rats, approximately 70% of an administered radioactive dose was excreted via this route, supporting the bile as the origin of the fecal radioactivity. There were no apparent sex- or dose-related differences in the routes of excretion for fludioxonil. Examination of urine for metabolites of fludioxonil showed at least 20 metabolites, each comprising a minor fraction of the administered dose (0.1-3.1%).
870.7600 Dermal penetration	NA	NA

13544

R179164

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