

## ANNEXE 4





*done  
6/9/00  
F2D*

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

013294

OFFICE OF  
PREVENTION, PESTICIDES, AND  
TOXIC SUBSTANCES

**MEMORANDUM**

DATE: 22-MARCH-99

SUBJECT: PP#5E04526. Difenoconazole (CGA-169374 Sico<sup>®</sup> 259 EC Fungicide) in/on Imported Bananas and PP#2F4107. Difenoconazole (**Dividend<sup>®</sup>**) in/on Wheat and Animal RACs. **HED Risk Assessment.** PC Code: 128847. Barcodes: D234002 and D250092. Case 283543 and 286648.

FROM: Dana Vogel, Chemist *[Signature]* 3/25/99  
Susie Chun, Chemist *CBK 3/25/99*  
Albin Kocialski, Ph.D, Toxicologist  
RAB1/ HED (7509C)

THROUGH: Melba Morrow, D.V.M., Branch Senior Scientist *M. Morrow 3/29/99*  
RAB1/HED (7509C)

TO: Cynthia Giles-Parker/John Bazuin (PM Team 22)  
Registration Division (7505C)

Novartis has proposed tolerances for residues of the fungicide difenoconazole ([{(2S,4R)/(2R,4S)}/[(2R,4R)/(2S,4S)]1-{2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1H-1,2,4-triazole) in/on imported bananas. The proposed import banana tolerance, expressed as parent compound only, is 0.2 ppm.

Time-limited tolerances are established for residues of the fungicide difenoconazole on wheat and animal RACs, as a result of seed treatment. These tolerances expired on 12/31/98 and are as follows (40 §CFR 180.475):

Wheat Grain	0.1 ppm		Wheat Forage	0.1 ppm
Wheat Straw	0.1 ppm		Milk	0.01 ppm
Eggs	0.05 ppm		Fat*	0.05 ppm
Meat*	0.05 ppm		Meat By-Products*	0.05 ppm

\*of cattle, goats, horses, hogs, poultry, and sheep

A summary of the findings and an assessment of human health risk resulting from the proposed and time-limited uses for difenoconazole are provided in this document. This risk assessment is being developed to determine whether current time-limited tolerances can be converted to permanent tolerances and to support the establishment of new tolerances. The hazard assessment was provided by Albin Kocialski of Registration Action Branch 1 (RAB1), the product and residue chemistry data review and dietary risk assessment by Susie Chun of RAB1, the occupational/residential risk assessment by Dana Vogel of RAB1, and the water exposure assessment by James Hetrick of the Environmental Fate & Effects Division (EFED).

## TABLE OF CONTENTS

I.	EXECUTIVE SUMMARY .....	4
II.	SCIENCE ASSESSMENT .....	10
A.	Physical and Chemical Properties Assessment .....	10
1.	Identification of Active Ingredients .....	10
2.	Structural Formula (Difenoconazole) .....	10
3.	Physical and Chemical Properties .....	10
B.	Toxicology Assessment .....	13
1.	Hazard Assessment .....	13
a.	Acute Toxicity .....	14
b.	Subchronic Toxicity .....	15
c.	Chronic Toxicity and Carcinogenicity .....	16
d.	Developmental and Reproduction Toxicity .....	18
e.	Neurotoxicity .....	19
f.	Mutagenicity .....	19
g.	Metabolism .....	19
2.	Dose Response Assessment .....	20
a.	Reference Dose (RfD) .....	20
b.	Carcinogenicity Classification and Risk Quantification .....	20
c.	Other Toxicological Endpoints .....	21
i.	Acute Dietary .....	21
ii.	Occupational/Residential Exposure .....	22
3.	FQPA Considerations .....	24
a.	Neurotoxicity Data .....	24
b.	Determination of Susceptibility .....	24
c.	Recommendation for a Developmental Neurotoxicity Study .....	24
d.	Determination of the FQPA Factor .....	24
4.	Data Gaps .....	25
5.	Summary of Toxicology Endpoint Selection .....	25
6.	Dietary Exposure and Risk Assessment/Characterization .....	26
a.	Dietary Exposure (Food Sources) .....	26
i.	Proposed Uses .....	26
ii.	Nature of the Residue - Plants .....	27
iii.	Nature of the Residue - Animals .....	29
iv.	Residue Analytical Methods .....	29
v.	Multiresidue Methods .....	30
vi.	Storage Stability Data .....	31
vii.	Crop Field Trials .....	31
viii.	Processed Food/Feed .....	33
ix.	Meat, Milk, Poultry, Eggs .....	33
x.	Water, Fish, and Irrigated Crops .....	33
xi.	Food Handling .....	33
xii.	Confined Accumulation in Rotational Crops .....	34
xiii.	Field Accumulation in Rotational Crops .....	34
xiv.	Tolerance Reassessment Table .....	34
xv.	Anticipated Residues .....	34
xvi.	Codex Harmonization .....	35

b.	Dietary Exposure (Drinking Water Source) .....	35
i.	Surface Water Estimates .....	36
ii.	Ground Water Estimates .....	36
iii.	Input Data and Assumptions for Models .....	36
c.	Dietary Risk Assessment and Characterization .....	38
i.	Chronic Risk (TMRC) .....	38
ii.	Carcinogenic Risk .....	39
iii.	Acute Dietary Risk .....	40
iv.	Drinking Water Risk (Acute, Chronic, and Cancer) .....	41
7.	Occupational/Residential Exposure and Risk Assessment/Characterization ...	44
a.	Occupational and Residential Exposure .....	44
i.	Summary of Use Patterns and Formulations .....	44
ii.	Seed Treatment Exposures and Assumptions .....	44
iii.	Commercial Seed Treater Exposure Assessment .....	46
iv.	Farm Worker Exposures and Assumptions .....	47
v.	Farm Worker Exposure Assessment .....	48
vi.	Post-Application Exposures and Assumptions .....	49
b.	Occupational and Residential Risk Assessment/Characterization .....	49
i.	Risks from Dermal, and Inhalation Exposures for Seed Treaters ...	49
ii.	Risks from Dermal, and Inhalation Exposures for Farm Workers ...	50
iii.	Risk from Residential Exposure .....	50
iv.	Risk from Post-Application Exposure .....	50
v.	Incident Reports .....	50
8.	Aggregate Exposure and Risk Assessment/Characterization .....	51
a.	Acute Aggregate Exposure and Risk .....	51
b.	Short- and Intermediate-Term Aggregate Exposure and Risk .....	51
c.	Chronic Aggregate Exposure and Risk .....	52
d.	Cancer Aggregate Exposure and Risk .....	52
9.	Other Food Quality Protection Act (FQPA) Considerations .....	53
a.	Cumulative Risk .....	53
b.	Endocrine Disruption .....	54
c.	Determination of Safety .....	54
III.	ACTIONS REQUIRED BY PETITIONER .....	54
A.	Additional Data Requirements .....	54
1.	Toxicological Studies .....	54
2.	Chemistry .....	54
3.	Occupational and Residential Exposure .....	55

## I. EXECUTIVE SUMMARY

HED has conducted a risk assessment for difenoconazole in support of the establishment of permanent tolerances on wheat and imported bananas. The import tolerance on bananas is a new use, while the uses for wheat and animal RACs are currently registered in the U.S. with time-limited tolerances that expired 12/31/98. HED has evaluated toxicology and residue data for difenoconazole submitted by Novartis Corporation. **The data are adequate to support a Section 3 registration and the establishment of permanent tolerances in/on wheat and animal commodities and the import tolerance on bananas.**

Difenoconazole is a systemic fungicide. It can be used foliarly or as a seed treatment. For the purposes of this action, liquid flowable concentrate and solid emulsifiable concentrate formulations are being supported.

The flowable concentrate is applied in a slurry of water, utilizing a mist-type application. This formulation is used as a seed treatment. The active ingredient difenoconazole is effective for the control of several seed and soil-borne fungi (common bunt, dwarf bunt, loose smut, flag smut, seed-borne septoria, fall season powdery mildew, septoria leaf blotch and rust, and for partial control of fusarium root and crown rot and common root rot) in grain seeds, such as wheat, barley, cotton, and sweet corn seed.

The emulsifiable concentrate is applied in an emulsion of oil. For PP5E4526, this formulation is the product used as a foliar treatment on imported bananas. It is currently registered for use in Belize with pending tolerances in Central America, Colombia, Ecuador, and Mexico. Difenoconazole is also registered for use on imported barley and rye.

Novartis currently has several registered labels for different formulations of Dividend. Some of these labels indicate special formulations for on-farm use (EPA reg.#s 100-777, 100-778, 100-885). There are two products for the wheat petition, one for wheat seed (EPA reg. # 100-740) and one for the technical product (EPA reg. # 100-739). The label for Dividend™ (EPA reg.# 100-740) is strictly for commercial seed treatment and contains the highest amount of active ingredient applied. Therefore, this label was used to develop the occupational exposure estimates. None of the labels have uses that could result in residential exposure.

### *Hazard Assessment*

The toxicological data base for difenoconazole is adequate to support a Section 3 registration.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is considered to be a mild eye irritant and a slight skin irritant and is not a dermal skin sensitizer.

Subchronic studies in mice and rats manifested decreased body weights, decreased body weight gains and effects on the liver at 200 ppm and higher. Microscopic examination of the eyes of dogs at 3000 ppm (revealed unilateral and bilateral lenticular cataracts in both sexes of animals). Decreased body weights, body weight gains, and food consumption was reported in a 21 day

rabbit dermal study at the LOAEL (Lowest Observable Adverse Effect Level) of **100 mg/kg/day**.

Chronic studies in rats revealed decreased body weight gains and increased liver weights along with hepatocellular hypertrophy. Clinical chemistry data supported the liver pathology data suggesting that the liver was the primary target organ. There were no treatment related neoplastic effects. The LOAEL was **500 ppm** (equal to 24.12 and 32.79 mg/kg/day for males and females respectively) and the NOAEL (No Observable Adverse Effect Level) was **20 ppm** (equal to 0.96 and 1.27 mg/kg/day for males and females respectively).

Chronic feeding studies in mice showed decreased body weight gains in male and female mice at termination. Treatment related non-neoplastic lesions were confined to the liver and were supported by the clinical chemistry data at a level of 300 ppm (46.29 and 57.79 mg/kg/day for males and females respectively). Liver tumors were observed in mice at 300 ppm and higher; however, based on the excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at the two lower doses of 10 and 30 ppm and the absence of genotoxic effects, the Cancer Peer Review Committee (CPRC) (Memo, Jess Rowland and Esther Rinde, 7/27/94) recommended for a cancer classification of C (**possible human carcinogen**) and advocated a MOE approach in risk assessment utilizing the NOAEL of **30 ppm** (4.7 and 5.6 mg/kg/day in males and females respectively) and the LOAEL of **300 ppm** (46.3 and 57.8 mg/kg/day in males and females respectively) from the mouse study using only those biological endpoints which were related to tumor development (i.e. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). However, at this time, the Agency has not defined the level of concern for cancer using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the  $Q_1^*$  approach. The  $Q_1^*$  was determined to be  $1.57 \times 10^{-1}$  (mg/kg/day)<sup>-1</sup>. This value incorporates the 3/4 scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunzman, 12/8/98).

Chronic studies in dogs revealed decreased body weight gains throughout the study at 500 ppm and increased levels of alkaline phosphatase at 1500 ppm (51.2 and 44.3 mg/kg/day for males and females respectively) The LOAEL was **500 ppm** (equal to 16.4 and 19.4 mg/kg/day for males and females respectively) and the NOAEL was **100 ppm** (equal to 3.4 and 3.7 mg/kg/day for males and females respectively).

The results of the 2-generation reproduction and developmental studies did not demonstrate increased sensitivity to infants and children.

Neurotoxicity studies are not applicable as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that difenoconazole possesses neurotoxic properties. It is not structurally related to known neurotoxic compounds.

Mutagenicity studies indicated that difenoconazole was not mutagenic under the test conditions.

Metabolism studies in rats indicated that peak absorption occurred between 28 and 48 hours post-dosing. Elimination in the feces ranged between 78 and 94% and in the urine between 8 and 21%. Difenoconazole did not accumulate to any appreciable extent since tissues contained less

than 1.0% of the radioactivity after 7 days post dosing. Difenoconazole undergoes successive oxidation and conjugation reactions. There is saturation of the metabolic pathway at high doses. The distribution, metabolism and excretion of difenoconazole are not sex dependent.

On September 8, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of difenoconazole, reconfirmed the Reference Dose (RfD), addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996, and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments (there are no residential uses at this time for difenoconazole). The FQPA Safety Factor Committee met on 10/19/98 and addressed the potential enhanced sensitivity to infants and children as required by FQPA and recommended for removal of the 10x FQPA Safety Factor.

#### *Dose Response Assessment*

For the acute dietary exposure and risk assessment, an acute dietary RfD of **0.25 mg/kg/day** was established for females 13+ years old. This selection was based on developmental effects in rabbits at the LOAEL of **75 mg/kg/day**. The NOAEL was determined to be **25 mg/kg/day**. There was no acute dietary RfD selected for the general population (including infants and children) as there were no effects observed in oral toxicology studies that could be attributable to a single oral dose.

For the chronic dietary exposure and risk assessment, the chronic RfD was established based on a combined chronic/toxicity/carcinogenicity study in rats. The NOAEL of **20 ppm** (equal to **0.96 mg/kg/day**) was based on reduction in body weight gains and hepatocellular hypertrophy at the LOAEL of **500 ppm** (equal to **24.12 mg/kg/day**). The chronic RfD was established at **0.01 mg/kg/day** based on inter species extrapolation (10x), and the intra species variability (10x).

The HIARC determined that both short-term and intermediate-term risk assessments are required for this use on wheat. The short-term dermal exposure was based on the rabbit developmental toxicity study even though a 21-day rabbit dermal study was available. As reproductive/fetal parameters are not evaluated in the dermal toxicity study, the consequences on these endpoints can not be ascertained for the dermal route of exposure. A 2-generation reproduction study was selected for intermediate-term dermal exposure. The HIARC determined that the effects seen in this study are of concern. These effects are not evaluated in the 21-day dermal study and are appropriate for risk assessment. Since an oral toxicity study was selected for both short- and intermediate-term dermal exposure and risk analysis, a dermal absorption factor of **75%** should be used in the calculation of the dermal risk assessment. A long-term dermal exposure assessment is not required based on a one time application as a seed treatment.

The HIARC determined that an inhalation risk assessment is not required for non-cancer endpoints. This is based on the low acute toxicity of the chemical (Toxicity Category IV), the application rate (**0.5-1.0 fl. oz./100 lbs of seed**) the application method (standard slurry or mist-type seed treater) and the number of applications (1x).



## *Dietary Risk Estimates from Food Sources*

### Chronic Dietary Risk (TMRC)

The RfD used for the chronic dietary analysis for difenoconazole is **0.01 mg/kg bwt/day**. A chronic dietary exposure analysis was performed [DEEM™ software, USDA 1989-91 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII)] . The dietary exposure analysis was a refined estimate, using anticipated residues from crop field trial data and percent crop treated data from the Biological and Economics Analysis Division (BEAD) (dated 2/9/99, 12/17/98) for some commodities to estimate the dietary exposure for the general population and 28 subgroups. The chronic dietary exposure for all population subgroups was less than 1% of the RfD. The chronic dietary risk for difenoconazole does not exceed the Agency's level of concern.

### Acute Dietary Risk

The HIARC recommended an acute dietary endpoint for females 13+ years old based on in utero effects. The acute dietary exposure for the subgroup females 13+ years old represents less than 1% of the RfD. This is a highly conservative risk estimate based on tolerance level residues and 100% crop treated. These values are below the Agency's level of concern. A dose and endpoint were not selected for the general population (including infants and children) because there were no in utero effects observed in the oral toxicological studies including maternal toxicity and developmental toxicity studies in rats and rabbits attributable to a single-dose.

### Cancer Dietary Risk

A cancer dietary exposure analysis was performed (DEEM™ software, USDA 1989-91 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII)) using anticipated residues from crop field trial data and percent crop treated data from BEAD for some commodities to estimate lifetime cancer risk for the general population. The lifetime risk was  $8.4 \times 10^{-7}$  for a 70-year exposure.

## *Dietary Risk Estimates from Drinking Water Sources*

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs. The Agency uses DWLOCs internally in the risk assessment process as a surrogate measure of potential pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

Tier I estimated environmental concentrations (EECs) were calculated for both surface water (GENEEC model) and ground water (SCI-GROW). Estimated average concentration of difenoconazole in ground water is **0.00084 ppb**. Estimated maximum concentrations of acute and chronic exposure to difenoconazole in surface water are **0.125 ppb** and 0.048 ppb, respectively. According to OPP drinking water guidance (HED SOP 98.4), the 90/56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment would be **0.016 ppb**. Tier I models represent the most conservative estimates of potential residues in drinking water. The drinking water assessment for difenoconazole is tentative because there are insufficient data to complete a quantitative environmental fate and transport assessment using Tier 1 FQPA models. Since difenoconazole is used solely as a fungicide on the seed coat of small grains to control soil-borne fungi, it is not expected to pose a major threat to ground and surface waters. These modeling assumptions are expected to yield highly conservative estimates for difenoconazole concentrations in drinking water. DWLOCs for acute, chronic (non-cancer), and cancer dietary risk from drinking water were calculated. Estimated environmental concentrations (EECs) from EFED for both surface and ground water did not exceed the chronic and acute DWLOCs.

#### *Occupational and Residential Risk Estimates*

HED does not currently perform an occupational exposure assessment for imported crops. Therefore, an occupational exposure assessment related to the foliar treatment of imported bananas was not performed. This exposure assessment only deals with the commercial wheat seed treatment scenario and resulting exposures from treated seed.

Based on the wheat uses of difenoconazole, the potential for occupational exposures exists. No potential for residential exposure exists. For this action, occupational exposure to difenoconazole is limited to the workers involved in the commercial seed treatment use. The corresponding label (EPA reg. # 100-740) strictly prohibits the use of this product at the farm site. All seed treatment with difenoconazole will be done indoors at a seed treatment facility.

In the agricultural setting, wheat planting usually consists of the following functions; mixer/loader and driver/planter. The highest amount of exposure will be for the mixer/loader scenario, opening the treated seed bags and emptying the contents into the application equipment.

The HIARC determined that inhalation risk assessments are not required since toxicological concerns were not identified via this route of exposure. Exposures from post-application residues of difenoconazole are not expected to pose any risks.

Only short- and intermediate-term dermal exposure is expected for the wheat use due to the limited number of applications per year. Long-term exposure is not expected for use of difenoconazole on agricultural, and non- agricultural areas due to one-time application. Hence, a long-term risk assessment was not conducted.

Exposure calculations were only done for the mixer/loader scenario because this scenario represents the highest possible exposure and therefore risk. Risk for the planter/driver is not

expected to exceed that of the mixer/loader. All risk estimates for the mixer/loader scenario are well below the Agency's level of concern.

Cancer risk endpoint established for the active ingredient is a  $Q_1^*$  of 0.157 mg/kg/day (Memo, Lori Brunzman, 12/8/98). Using the  $Q_1^*$  approach, HED's level of concern for occupational cancer risk for commercial seed treaters and farm workers does not exceed HED's level of concern. The calculated cancer risk is not expected to exceed  $8.2 \times 10^{-5}$  and  $3.1 \times 10^{-6}$  for the seed treaters and farm worker, respectively.

#### *Aggregate Risk Estimates*

Aggregate risk is estimated by combining dietary (food and water) and residential exposures. There are no residential uses for difenoconazole. Therefore, aggregate risk estimates were based on the exposure from food and water only for the most highly exposed population subgroups and the general population as appropriate. For the acute dietary exposure to difenoconazole, conservative assumptions were used to estimate risk; i.e., dietary assessment -100% crop treated and residues at tolerance levels, water-Tier 1 and maximum application rate. For chronic and cancer, the dietary exposure analyses were refined estimates, using anticipated residues from crop field trial data and percent crop treated data from the Biological and Economics Analysis Division (BEAD) (dated 2/9/99, 12/17/98) for some commodities to estimate the dietary exposure for the general population and 28 subgroups.

HED concludes with reasonable certainty that the proposed use of difenoconazole will not result in unacceptable levels of aggregate acute, chronic, or cancer human health risk for any subgroup of the population at this time. Based on the available data and assumptions used for acute dietary/water exposure and risk estimates, the population group estimated to be the most highly exposed to difenoconazole is females (13+ years old). The cancer aggregate risk for the general population was calculated as an MOE of 8400. At this time, the Agency has not defined the acceptable level of concern for cancer risk using the MOE approach. Therefore, a  $Q_1^*$  was calculated to estimate potential cancer risk (Memo, Lori Brunzman, 12/8/98). Using the  $Q_1^*$  approach, the cancer risk was below HED's level of concern. The Agency has calculated DWLOCs for acute exposure to difenoconazole in drinking water for females (13+ years old, nursing) to be **7500 ppb**. For chronic (non-cancer), the DWLOCs are **350** and **100 ppb** for U.S. population and non-nursing infants (< 1 year old), respectively. For cancer exposure to difenoconazole, the adult DWLOC is 0.048 ppb. The surface water EEC were **0.125 ppb** for acute and **0.048 ppb** for chronic. The ground water EEC was **0.00084 ppb**. These values are below HED's DWLOCs.

Since there are no registered uses that will result in residential exposures for difenoconazole, short- and intermediate-term aggregate risk assessments were not conducted.

#### Recommendation for Tolerances

Adequate residue chemistry and toxicology data have been submitted to support the establishment of the following permanent tolerances for residues of parent difenconazole:

Bananas	0.2 ppm
Wheat Grain	0.1 ppm
Wheat Forage	0.1 ppm
Wheat Straw	0.1 ppm
Milk	0.01 ppm
Eggs	0.05 ppm
Fat*	0.05 ppm
Meat*	0.05 ppm
Meat By-Products*	0.05 ppm

\*of cattle, goats, horses, hogs, poultry, and sheep

## II. SCIENCE ASSESSMENT

### A. Physical and Chemical Properties Assessment

#### 1. Identification of Active Ingredients

Chemical Name: ((2S,4R)/(2R,4S))/[(2R,4R)/(2S,4S)]1-{2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1H-1,2,4-triazole)

Common Name: Difenoconazole

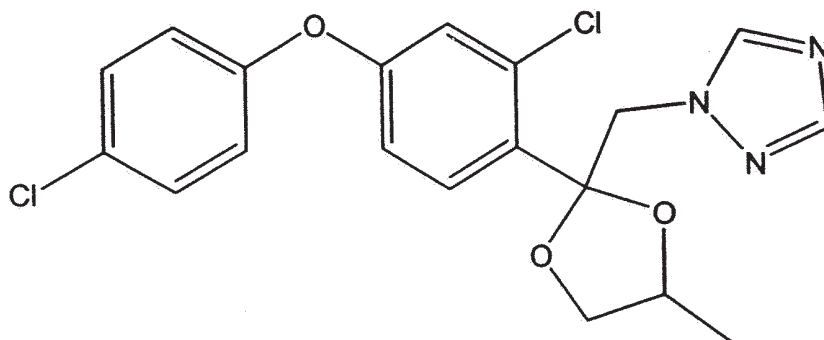
PC Code Number: 128847

CAS Registry No.: 119446-68-3

Empirical Formula: C<sub>19</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>

Molecular Weight: 405.06

#### 2. Structural Formula (Difenoconazole)



#### 3. Physical and Chemical Properties

Product chemistry data for the difenoconazole technical product were reviewed (Memo, D172067, R. Lascola, 10/26/92; Memo, G. Kramer, D194842, 3/30/94;

Memo, G. Kramer, D203644, 6/16/94; Memo, G. Kramer, D210080, 1/19/95) and deemed adequate to fulfill the requirements for a Section 3 permanent tolerance request. No additional product chemistry data are required for the purposes of this permanent tolerance request.

Table 1. Product Chemistry

Requirement	Results <sup>a</sup>	MRID Number
Color	beige -greyish	420900-03
Physical State	crystalline	420900-03
Odor	sweetish	420900-03
Melting Point	78.6°C	420900-03
Boiling Point	N/A <sup>b</sup>	
Density, Bulk Density or Specific Gravity	1.37 g/cm <sup>3</sup> typical at 20°C	420900-03
Solubility	Solubilities (g/100 mL at 25°C, except as noted): water: 3.3 ppm @ 20°C 1-octanol: 25 acetone: 88 ethanol: 89 toluene: 77 n-hexane: 0.5	420900-03
Vapor Pressure	2.5 x 10 <sup>-10</sup> mm Hg @ 25°C	420900-03
Dissociation Constant	pK <sub>a</sub> < 0	420900-03
Octanol/Water Partition Coefficient	log K <sub>ow</sub> = 4.2 @ 25°C	420900-03
pH	6-8 typical at 20°C (saturated solution)	420900-03

Table 1. Product Chemistry

Requirement	Results <sup>a</sup>	MRID Number
Stability	<p>Original comp.: 94.5%</p> <p>At 20-25°C:</p> <p>6 months: 94.4%</p> <p>12 months: 94.3%</p> <p>24 months: 95.5%</p> <p>At 35°C:</p> <p>3 months: 95.1%</p> <p>6 months: 94.7%</p> <p>12 months: 94.9%</p> <p>24 months: 95.1%</p> <p>At 54°C:</p> <p>0.5 months: 93.1%</p> <p>3 months: 94.9%</p> <p><u>Stability to metals:</u> The solid TGA1 was stored in tin cans or exposed to strips of stainless steel, carbon steel and aluminum. Test samples were stored at room temperature or 38 °C. Samples were analyzed after 8, 16 and 26 weeks by visual inspection and GC analysis. No decomposition of the TGA1 was observed.</p> <p><u>Stability to sunlight:</u> The solid TGA1 was exposed to simulated sunlight (Xenon arc lamp) for 24 hours. Visual inspection and chromatographic analysis demonstrated that no decomposition of the TGA1 had occurred.</p> <p><u>Stability to metal ions:</u> The TGA1 was stored in 10% solutions of zinc sulfate, copper (II) sulfate, aluminum sulfate and iron (II) sulfate for 3 days at 20 or 38°C. The pH ranged from 3-4.4. The TGA1 appeared to be stable in the presence of all ions except ferrous ion, in which a 3-4% decrease in difenoconazole concentration was observed.</p>	<p>428065-03</p> <p>432365-03</p> <p>434679-01</p>
Oxidizing or Reducing Action	N/A <sup>b</sup>	422451-01
Flammability	N/A <sup>b</sup>	422451-01
Explodability	N/A <sup>b</sup>	422451-01
Storage Stability	N/A <sup>b</sup>	422451-01
Viscosity	N/A <sup>b</sup>	422451-01
Miscibility	N/A <sup>b</sup>	422451-01
Corrosion Characteristics	N/A <sup>b</sup>	422451-01

<sup>a</sup> N/A = Not Applicable.

<sup>b</sup> Data are not required for the TGA1.

## B. Toxicology Assessment

### 1. Hazard Assessment

**Table 2. Subchronic/Chronic/Mutagenicity /Metabolism/Toxicity of Difenoconazole**

Study Type	MRID No.	Results
21-day dermal toxicity-rabbit	42090013	NOAEL=10 mg/kg/day LOAEL=100 mg/kg/day
13 week feeding mouse	42090021	NOAEL=2 mg/kg/day LOAEL=30.8 mg/kg/day
13 week feeding rat	42090022	NOAEL=1 mg/kg/day LOAEL= 37.5 mg/kg/day
26 week oral feeding dogs	42090012	NOAEL=31.3 mg/kg/day LOAEL=96.6 mg/kg/day
carcinogenicity study mouse	42090015; 42710006	NOAEL(systemic)=4.7 mg/kg/day LOAEL(systemic)= 46.3 mg/kg/day liver tumors in males/females
chronic toxicity/carcinogenicity in the rat	42090019;20	NOAEL=0.96 mg/kg/day LOAEL=24.12 mg/kg/day no evidence of carcinogenicity
chronic toxicity study dog	42090014; 42710005	NOAEL=3.4 mg/kg/day LOAEL=16.4 mg/kg/day
developmental toxicity rat	42090016	mater NOAEL=20 mg/kg/d LOAEL=100 mg/kg/d devel NOAEL=100 mg/kg/d LOAEL=200 mg/kg/d
developmental toxicity rabbit	42090017	mater NOAEL=25 mg/kg/d LOAEL=75 mg/kg/d devel NOAEL=25 mg/kg/d LOAEL=75 mg/kg/d
reproductive toxicity	42090018	parent NOAEL=1.25 mg/kg/day LOAEL=12.5mg/kg/d offspg NOAEL=1.25 mg/kg/day LOAEL=12.5mg/kg/d

Study Type	MRID No.	Results
gene mutation-Salmonella	42090025	non-mutagenic +/- activation
gene mutation-E.coli	42710011	non-mutagenic +/- activation
micronucleus assay	42710012	non-mutagenic
DNA repair assay	42710012	non-mutagenic +/- activation
metabolism rat	42090028-31; 42710013-14	Distribution,metabolism, excretion not sex dependent. 78-94% found in feces and 8-21% in urine. No accumulation. Negligible residues in tissues at 7 days. Peak absorption at 24- 48 hrs. Saturation of metabolic pathway at high doses.

**a. Acute Toxicity**

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is considered to be a mild eye and slight skin irritant and is not a dermal sensitizer. It is not neurotoxic. Table 2 and 3 summarize the toxicity studies and the categories of toxicity of this chemical.

**Table 3. Acute Toxicity of Difenoconazole Technical**

Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
81-1	Acute Oral	42090006	LD <sub>50</sub> =1453 mg/kg	III
81-2	Acute Dermal	42090007	LD <sub>50</sub> =>2010 mg/kg	III
81-3	Acute Inhalation	42090008	LC <sub>50</sub> =>3300 mg/m <sup>3</sup> [4 hrs. Exposure]	IV
81-4	Primary Eye Irritation	42090009	mild eye irritation reversible in 7 days	III
81-5	Primary Skin Irritation	42090010	slight irritant	IV
81-6	Dermal Sensitization	42090011 42710004	negative	NA



## b. Subchronic Toxicity

The subchronic oral studies in rats and dogs satisfy the guideline requirements.

**13 week feeding study in mice** (MRID# 42090021). Five groups of CD-1 (ICR) mice composed of 15 animals /sex/dose and 20 mice /sex/controls were fed dietary concentrations of either 0, 20, 200, 2500, 7500, or 15000 ppm of 94.5% pure difenoconazole for 13 weeks (equal to 0, 2.9, 30.8, 383.6, 1125, and 2250 mg/kg/day in males and 0. 4.4, 41.5, 558.9, 1125, 2250 mg/kg/day in females). Nearly all mice fed 7500 or 15000 ppm difenoconazole died during the first week of the study. Statistical analysis of food consumption and body weight changes over the course of the study for the remaining groups showed significantly decreased body weight gain for animals receiving 2500 ppm and a significant negative trend. Compound related effects from histological examination were confined to the liver. Mice that survived to the end of the study showed hepatotoxicity that included hepatocellular enlargement and vacuolation in animals receiving 2500 ppm as well hepatocyte enlargement in animals given 200 ppm of compound. The LOAEL was concluded to be 200 ppm based on decreased body weight gains and liver histopathology. The NOAEL was 20 ppm (equivalent to 2.0 mg/kg in males and 4.4 mg/kg in females).

**13-week feeding study in rats** (MRID# 42090022). Difenoconazole (94.5%) was administered orally in feed to CRL:CD(SD) rats at dose levels of 0, 20, 200, 750, 1500 and 3000 ppm (equivalent to 0, 1, 10, 37.5, 75, and 150 mg/kg/day) for 13 weeks. There were 20 animals/sex/dose in the control group and 15 animals/sex/dose in each of the test groups. The LOAEL was 200 ppm (10 mg/kg/day) based on a 10% decrease in the body weights of females (concurrent with a negative trend for food consumption). The LOAEL in males was 750 ppm (equivalent to 37.5 mg/kg/day) based on increases in the absolute liver weights. The NOAEL was 20 ppm (equivalent to 1 mg/kg/day).

**Twenty-six week oral feeding study in dogs** (MRID# 42090012). Difenoconazole (94.5% pure) was given in feed to five groups of pure bred beagle dogs composed of 3 animals/sex/dose in dietary concentrations of 0, 100, 1000, 3000 or 6000 ppm (equal to mean daily doses of 0, 3.4, 34.8, 110.6, and 203.7 mg/kg/day for females and 0, 3.6, 31.3, 96.6, and 157.8 mg/kg/day for males). The LOAEL was considered to be 3000 ppm based on unilateral or bilateral lenticular cataracts seen under microscopic examination in all three female dogs and one of three male dogs which was the only species to show this effect. The NOAEL was concluded to be 1000 ppm (31.3 to 34.0 mg/kg/day).

**Twenty-one day dermal toxicity study in rabbits** (MRID# 42090013). Difenoconazole (94.4% pure) was administered topically under occlusion to three groups of New Zealand White rabbits (5/sex/dose) at daily dose of 10, 100, or 1000 mg/kg/day for six hours a day for 21 consecutive days. An additional group served as vehicle control. No animals died on study. The LOAEL was

determined to be **100 mg/kg/day** based on statistically significant decrements in body weight, body weight gain, and food consumption. The NOAEL was **10 mg/kg/day**.

**c. Chronic Toxicity and Carcinogenicity**

The chronic and carcinogenicity studies in rats, dogs, and mice satisfy the guideline requirements for both the chronic and carcinogenicity studies.

**Combined chronic toxicity and carcinogenicity study in rats** (MRID# 42090019;20). Difenoconazole (94.5% pure) was administered in the diet to male and female Sprague-Dawley rats (80/sex/dose) for 104 weeks at dose levels of 0, 10, 20, 500, and 2500 ppm (equal to 0, 0.48, 0.96, 24.12, or 123.7 mg/kg/day in males and 0, 0.64, 1.27, 32.79, or 169.6 mg/kg/day in females) for 104 weeks. Body weight gains were reduced in groups receiving 500 and 2500 ppm of test compound. Mean liver weights were increased at week 53 and at termination in animals given 2500 ppm. Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm group at termination. Clinical chemistry data supported the pathology data in that the liver was the primary target organ. There were no treatment related increased incidences of neoplastic findings observed in this study. The LOAEL was determined to be **500 ppm** equal to **24.12 mg/kg/day** and **32.79 mg/kg/day** for males and females respectively based on reductions in body weight gains and hepatocellular hypertrophy. The NOAEL was **20 ppm** equal to **0.96** and **1.27 mg/kg/day** for males and females, respectively.

**Chronic toxicity study in the dog** (MRID# 42090014; 42710005). Forty male and female dogs were divided into five animals/sex/dose and fed dietary concentrations of either 0, 20, 100, 500 or 1500 ppm (equal to 0, 0.71, 3.4, 16.4, 51.2 mg/kg/day for males and 0, 0.63, 3.7, 19.4, and 44.3 mg/kg/day) of 94.5% difenoconazole for 52 weeks. Females receiving 1500 ppm in the diet had a significant reduction in body weight gain on day seven and inhibited but not statistically significant body weight gains at 500 and 1500 ppm throughout the remainder of the study. Food consumption was also sporadically decreased throughout the study. Significant increases were also noted for alkaline phosphatase in males given 1500 ppm. There were no compound related effects associated with either gross or microscopic pathology. The LOAEL was **500 ppm** based on decreased body weight gains through out the study as well as decreased food intake. The NOAEL was **100 ppm** (3.4 to 3.7 mg/kg/day).

**Carcinogenicity study in mice** (MRID# 42090015; 427100006). Groups of 60-70 male and female Crl:CD-1 mice were fed diets of difenoconazole (94.5% pure) at concentrations of either 0, 10, 30, 300, 2500, or 4500 ppm (equal to 0, 1.5, 4.7, 46, 423, and 819 mg/kg/day in males and 0, 2, 6, 58, and 512 mg/kg/day in females) for 78 weeks. All females receiving 4500 ppm died within the first two weeks of the study. A statistically significant increasing trend in mortality was noted for males but not for females. Food consumption was comparable between control and

treated groups; however body weight gain when compared to controls for male mice at termination revealed decreases of 12, 10 and 34 percent at dose levels of 300, 2500 and 4500 ppm and in females body weight gain values were 7 and 22 percent lower when compared to controls. Alterations in clinical chemistry were manifested as elevations in alanine aminotransferase, sorbitol dehydrogenase, and serum alkaline phosphatase in males at 2500 and 4500 ppm and in females at 2500 ppm. Treatment related non-neoplastic lesions were confined to the liver at 300 ppm and above in males and females (necrosis of individual hepatocytes, focal and multi focal necrosis, hepatocellular hypertrophy, inflammation, bile stasis, and fatty changes).

Male mice had significant ( $p < .01$ ) increasing trends in hepatocellular adenomas, carcinomas and combined adenomas and carcinomas. Pair wise comparison showed a significant ( $p < .05$ ) increase in hepatocellular adenomas at 300 and 2500 ppm when compared to controls as well as at 4500 ppm. Pair wise comparisons also showed increases ( $p < .01$ ) at 4500 ppm in males for adenomas, carcinomas and adenomas and carcinomas combined. Female mice had a dose related trend ( $p < .01$ ) for adenomas, carcinomas and for combined tumors. Pair wise comparisons at 2500 ppm for females reached statistical significance for adenomas ( $p < .01$ ), carcinomas ( $p < .05$ ) and for tumors combined ( $p < .01$ ). The CPRC determined (Memo, J. Rowland and Esther Rinde, 7/27/94) that the two high doses of 2500 and 4500 ppm were excessive in both sexes and also determined that there was significant toxicity (including liver necrosis) at 300 ppm in the male mice; this dose also had a significant increase in liver adenomas. The remaining doses (10 and 30 ppm) did not have statistically significant increases in liver tumors. Since there were no doses between 300 and 2500 ppm and because of the excessive toxicity at the two highest doses the CPRC concluded that this may not have been an appropriate test. Therefore based on the increased incidence of liver tumors in both sexes of mice, by both pair wise and trend analysis, consideration of the excessive toxicity at the two high doses, the absence of genotoxicity concern, the CPRC recommended for the margin-of-exposure approach (MOE) for the quantification of human risk utilizing the NOAEL/LOAEL from the mouse study. It was therefore determined that a NOAEL of 4.7 mg/kg/day and a LOAEL of 46.3 mg/kg/day would be used in the MOE calculations using only those biological endpoints which were related to tumor development (non-neoplastic hepatic lesions) which were hepatocellular hypertrophy, necrosis, fatty changes and bile stasis in mice (and hyper cellular hypertrophy in rats). The LOAEL is 46.3 based on hepatocellular hypertrophy, hepatocellular adenomas, necrosis, fatty changes and bile stasis. The NOAEL was 4.7 mg/kg/day). However, at this time, the Agency has not defined the acceptable level of concern for cancer risk using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the  $Q_1^*$  approach. The  $Q_1^*$  was determined to be  $1.57 \times 10^{-1}$  (mg/kg/day)<sup>-1</sup>. This value incorporates the 3/4 scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunsman, 12/8/98).

#### **d. Developmental and Reproduction Toxicity**

**Developmental toxicity study in rats** (MRID# 42090016). Difenoconazole was administered to Crl:COBS CD (SD) pregnant rats at dose levels of 0, 2, 20, 100, or 200 mg/kg/day from days 6-15 of gestation. Statistically significant decreases in maternal body weight gain and feed consumption were observed during the dosing period at dose levels of 100 and 200 mg/kg/day. Body weight gain decreases of 21% and 57% were recorded for the 100 and the 200 mg/kg/day dose groups for days 6-15. At 200 mg/kg/day the incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on a fetal basis. There were also significant increases in the average number of ossified hyoid and decreases in the number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased with accompanying increases in the number of thoracic vertebrae and decreases in the number of lumbar vertebrae in this group. (The DER indicates that these findings at the highest dose tested of 200 mg/kg/day appear to be the result of maternal toxicity). The NOAEL for maternal toxicity was 20 mg/kg/day and the LOAEL for maternal toxicity was determined to be 100 mg/kg/day based on decreased body weight gains and decreased food consumption at 100 mg/kg/day and higher. The NOAEL for developmental toxicity was 100 mg/kg/day and the LOAEL 200 mg/kg/day based on the incidence of bifid or unilateral ossification of the thoracic vertebrae which was significantly increased on a fetal basis, and the significant increases in the average number of ossified hyoid and decreases in the number of sternal centers of ossification (per fetus per litter). The average number of ribs was also significantly increased with accompanying increases in the number of thoracic vertebrae and decreases in the number of lumbar vertebrae in this group.

**Developmental toxicity study in rabbits** (MRID# 42090017). In a developmental toxicity study, impregnated rabbits (16/dose) were given oral administration of difenoconazole at 0, 1, 25, or 75 mg/kg/day during days 7 through 19 of gestation. At 75 mg/kg/day, maternal toxicity was manifested as decreased body weight gain and food consumption; no maternal toxicity was observed at lower doses. Developmental toxicity observed only at 75 mg/kg/day was a slight non-significant increase in post-implantation loss and resorptions/doe and a significant decrease in fetal weight. For maternal toxicity, the LOAEL of 75 mg/kg/day is based on decreases in body weight gain and food consumption; the NOAEL is 25 mg/kg/day. For developmental toxicity, the LOAEL of 75 mg/kg/day is based on increases in post-implantation loss and resorptions per doe and decreases in fetal body weight; the NOAEL is 25 mg/kg/day.

**Two generation reproduction study in rats** (MRID# 42090018). In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm (0, 1.25, 12.5, or 125 mg/kg/day, respectively). Statistically significant reductions in body weight gains of F<sub>0</sub> and F<sub>1</sub> males were observed at 2500 ppm during Days 70-77 and during the course of the study (terminal body weight minus Day 0 body weight). Significant reductions in

body weight gains of F<sub>0</sub> and F<sub>1</sub> females were seen during the pre-mating, gestation, and lactation periods. A dose-related, but non-statistically significant decrease in body weight gain was seen in F<sub>0</sub> females at 250 ppm during Days 70-77 prior to mating, Days 0-7 of gestation, and Days 7-14 of lactation. At 2500 ppm, significant reductions in pup body weight were detected on Days 0, 4 (pre- and post culling), 7, 14, and 21 for males and females of both generations. There was a significant reduction in the body weight of F<sub>1</sub> male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F<sub>1</sub> generation surviving Days 0-4 was significantly reduced in the 2500 ppm group. For parental toxicity, the LOAEL of 250 ppm (12.5 mg/kg/day) is based on the decreased maternal body weight gain; the NOAEL is 25 ppm (1.25 mg/kg/day). For reproductive toxicity, the LOAEL of 250 ppm (12.5 mg/kg/day) is based on decreased pup weights at Day 21; the NOAEL is 25 ppm (1.25 mg/kg/day).

#### e. Neurotoxicity

These studies are not applicable as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that difenoconazole possesses neurotoxic properties. It is not structurally related to known neurotoxic compounds.

#### f. Mutagenicity

**Mutagenicity** (MRID# 42090025;42710011;-12). Difenoconazole was not mutagenic with or without metabolic activation when tested at concentrations ranging from 340 to 5447 micrograms/plate in two independently performed microbial/mammalian microsome plate incorporation assays using Salmonella typhimurium strains TA1535, TA1537, TA98, and TA 100 and Escherichia coli strain WP2uvrA. In an *in vivo* micro nucleus assay, no increase in micro nucleated polychromatic erythrocyte counts were seen in the bone marrow cells of mice given oral administration of difenoconazole at 0, 400, 800 or 1600 mg/kg/day. Difenoconazole was negative in an *in vitro* UDS assay with primary rat hepatocytes at concentrations up to 50.0 ug/mL.

#### g. Metabolism

**Metabolism** (MRID# 420900-28,29,30,31; 427100-13,14) Rats were administered a single oral gavage dose of 0.5 or 300 mg of <sup>14</sup>C difenoconazole or 0.5 mg/kg unlabeled difenoconazole by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg <sup>14</sup>C difenoconazole on day. From the proposed metabolic pathway of difenoconazole in rats, the compound undergoes successive oxidation and conjugation reactions (Carcinogenicity Peer Review of Difenoconazole, 5/18/94). One of the metabolites, CGA-205375, accounts for 6-24% of the applied dose and is found only in the urine and feces of high dose (300 mg/kg) rats. The presence of this intermediate in the excreta of only high dose rats, suggests that its rate of further biotransformation has reached saturation at the high dose. Additionally,

excretion of radioactivity in the bile, feces, and urine of rats orally dosed with <sup>14</sup>C-difenoconazole is consistent with saturation of the gastrointestinal absorption of the chemical at 300 mg/kg. The distribution, metabolism and excretion were not sex dependent. The elimination in the feces ranged between 78 and 94 % and in the urine from 8-21%. Peak absorption occurred between 24-48 hours for dosing groups. The study also indicated that the compound does not accumulate to any appreciable extent since tissues contained negligible residues (<1%) of radioactivity after 7 days post-exposure.

The metabolism study in the rat is acceptable and satisfies the guideline requirement for a metabolism study (85-1) in the rat.

## 2. Dose Response Assessment

On September 25, 1998, the Health Effects Division's HIARC report evaluated the toxicology data base of difenoconazole, reconfirmed the Reference Dose (RfD), addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996, and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments (there are no residential uses at this time for difenoconazole). The FQPA Safety Factor Committee report dated October 28, 1998 also addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The CPRC previously met on July 27, 1994 to evaluate the carcinogenic potential of difenoconazole.

### a. Reference Dose (RfD)

A chronic RfD of 0.01 mg/kg/day was established, based on the NOAEL of 0.96 mg/kg/day established in the 104 week chronic toxicity/carcinogenicity in rats and using an uncertainty factor of 100 (10x for inter-species extrapolation, 10x for intra-species variability). The LOAEL in this study, 24.12 mg/kg/day, was based on cumulative decreases in body weight gains.

### b. Carcinogenicity Classification and Risk Quantification

The Health Effects Division (HED) CPRC met on May 18, 1994 to discuss and evaluate the weight of evidence on difenoconazole with particular reference to its carcinogenic potential. The CPRC concluded that difenoconazole should be classified as a Group C - **possible human carcinogen** and recommended for the purpose of risk assessment, the margin-of-exposure (MOE) approach should be used for the quantification of human risk (Memo, Jess Rowland and Esther Rinde, 7/27/94).

The decision to classify difenoconazole as a Group C carcinogen was based on statistically significant increases in liver adenomas, carcinomas, and combined adenomas and carcinomas in both sexes of CD-1 mice, only at doses that were

considered to be excessively high for carcinogenicity testing. The MOE approach was recommended because there was only very weak (limited) evidence of carcinogenic potential at dose levels not considered to be excessive, with significant changes observed only at excessive doses. In addition there was no evidence of genotoxicity. Therefore a threshold model was recommended for the estimation of risk. Although both rats and mice showed adverse effects in the liver, it was recommended that the MOE be calculated from the NOAEL/LOAEL established in the mouse study, since a positive (cancer) response was seen in this species. Therefore, it was determined that a NOAEL of 4.7 mg/kg/day and a LOAEL of 46.3 mg/kg/day would be used in the calculations. The selection of a NOAEL for calculating risk utilizes only those biological endpoints which are related to tumor development (non-neoplastic hepatic lesions). The endpoints considered included: liver tumors, hepatocellular hypertrophy, necrosis, fatty changes, bile stasis in mice, and hepatocellular hypertrophy in rats. In addition, those doses levels represented the majority of the NOAELs and LOAELs for the endpoints examined. Most of the other NOAELs and LOAELs were higher than the one selected. However, at this time, the Agency has not defined the acceptable level of concern for cancer risk using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the  $Q_1^*$  approach. The  $Q_1^*$  was determined to be  $1.57 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ . This value incorporates the 3/4 scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunsman, 12/8/98).

**c. Other Toxicological Endpoints**

**i. Acute Dietary**

A dose and endpoint were selected for the population subgroup females 13+ years old for dietary risk assessment because there were effects attributable to a single dose (exposure) observed in rabbit developmental studies. The effects observed are presumed to occur after a single exposure and was therefore considered appropriate for this risk assessment since these are *in utero* effects. The dose and endpoint selected for this population subgroup was 25 mg/kg/day (NOAEL) based on post-implantation loss and resorptions per doe and a significant decrease in fetal weight at 75 mg/kg/day which was the LOAEL. The acute RfD was determined to be 0.25 mg/kg/day after utilizing a 100 fold uncertainty factor.

A dose and endpoint were not selected for the general population and infants and children as no effects of concern observed in oral toxicology studies, including maternal toxicity in the developmental toxicity studies in rats and rabbits, that were attributable to a single exposure (dose).

## ii. Occupational/Residential Exposure

### a) Dermal Absorption

A dermal absorption study is not available. Therefore, the HIARC estimated a dermal absorption factor based on the LOAEL established for the same endpoint in the oral developmental toxicity study in rabbits and the 21-day dermal toxicity study in rabbits. In the oral developmental toxicity study in rabbits, the maternal LOAEL was 75 mg/kg/day based on the decreased body weight gain and food consumption; the maternal NOAEL was 25 mg/kg/day (MRID# 42090017). In the 21-day dermal toxicity study in rabbits, the systemic toxicity LOAEL was 100 mg/kg/day based on decreases in body weight, body weight gain and food consumption; the NOAEL was 10 mg/kg/day (MRID# 420900-13).

The ratio of the LOAELs from the oral and dermal rabbit studies indicated an approximate dermal absorption rate of 75% ( $75 \div 100 = 75\%$ ).

Dermal absorption factor = 75%

### b) Short-Term (1-7 Days) Dermal

The effects observed in a developmental toxicity rabbit study were selected as an endpoint for a short-term dermal exposure. A 21-day dermal study in rabbits is available, however a developmental study was selected because: 1) the endpoint in the 21-day study was limited to changes in body weights and food consumption; 2) developmental effects were considered to be appropriate for this exposure period (1-7 days); 3) reproductive/fetal parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects can not be ascertained for the dermal route of exposure; and 4) the endpoint will provide adequate protection for the subpopulation female 13+ (i.e. pregnant workers). Since an oral NOAEL was selected, a dermal absorption factor of 75% should be used for this dermal risk assessment. NOAEL = 25 mg/kg/day based on post-implantation loss and resorptions/doe and a significant decrease in fetal weight at 75 mg/kg/day (LOAEL). This risk assessment is required.

### c) Intermediate-Term (7 days to several months) Dermal

A two generation reproduction study was selected for an intermediate-term dermal exposure. A 21-day dermal study in rabbits is available, however a reproduction study was selected because: 1) the endpoint in the 21-day study was limited to changes in body weights and food



consumption; 2) reproductive effects were considered to be appropriate for this exposure period (7 days to several months); 3) reproductive/fetal parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects can not be ascertained for the dermal route of exposure. Since an oral NOAEL was selected a dermal absorption factor of 75% should be used for this dermal risk assessment. The NOAEL was determined to be 1.25 mg/kg/day based on decreased pup weight at 12.5 mg/kg/day (LOAEL) on day 21. This risk assessment is required.

**d) Long-Term (several months to life) Dermal**

Long term dermal exposure is not expected based on a one time application as a seed treatment to wheat. This risk assessment is not required. Difenconazole was, however, classified as a Group C, possible human carcinogen with a recommendation for a non-linear (MOE) approach for human risk assessment (Memo, Jess Rowland and Esther Rinde, 7/27/94) Although both rats and mice showed adverse effects in the liver, the MOE would be calculated from the NOAEL/LOAEL established in the mouse study, since a positive (cancer) response was seen in this species. Therefore, it was determined that a NOAEL of 4.7 mg/kg/day and a LOAEL of 46.3 mg/kg/day would be used in the calculations. The selection of an NOAEL for calculating the MOE utilizes only those biological endpoints which are related to tumor development (non-neoplastic hepatic lesions). The endpoints considered included: hepatocellular hypertrophy, necrosis, fatty changes, bile stasis in mice, and hepatocellular hypertrophy in rats. A dermal absorption factor of 75% should be used for route-to-route extrapolation. However, at this time, the Agency has not defined the acceptable level of concern for cancer risk using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the  $Q_1^*$  approach. The  $Q_1^*$  was determined to be  $1.57 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ . This value incorporates the 3/4 scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunzman, 12/8/98).

**e) Inhalation Exposure (Any-Time period)**

This risk assessment is not required for non-cancer exposure as there is minimal concern for potential inhalation exposure/risk. This is based on the low acute toxicity of the chemical (Toxicity Category IV), the application rate (0.5-1.0 fl. oz./100 lbs of seed) the application method (standard slurry or mist-type seed treater) and the number of applications (1x).

### 3. FQPA Considerations

#### a. Neurotoxicity Data

These studies are not applicable as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that difenoconazole possesses neurotoxic properties. It is not structurally related to known neurotoxic compounds.

#### b. Determination of Susceptibility

Acceptable prenatal toxicity studies in rats and rabbits with difenoconazole have been submitted to the Agency. An acceptable reproductive toxicity study in rats with difenoconazole was also available. Hence, there were no data gaps for the assessment of the effects of difenoconazole following *in utero* exposure or the effects on young animals following early exposure. The data provided no indication of increased susceptibility of rats or rabbits to *in utero* or post-natal exposure to difenoconazole. (See preceding executive summaries for the relevant findings from the developmental toxicity and reproductive toxicity studies.)

#### c. Recommendation for a Developmental Neurotoxicity Study

The HIARC determined that a developmental neurotoxicity study in rats is not required based on the following factors:

- Difenoconazole is not structurally related to a neurotoxic agent.
- There is no evidence in the acute, subchronic or the chronic studies that difenoconazole induces neurotoxic effects.
- No increased susceptibility was seen in the prenatal developmental toxicity studies and in the pre/post natal reproductive toxicity study
- There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.

#### d. Determination of the FQPA Factor

HED's FQPA Safety Factor Committee met on October 19, 1998 (Memo, B. Tarplee, 10/28/98) to evaluate the hazard and exposure data for difenoconazole to ensure the protection of infants and children from exposure to this chemical. The Committee recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) should be reduced to a 1x factor.

The Committee recommended that the 10x safety factor be reduced since:

- 1) The toxicology data base is complete.
- 2) There is no indication of increased susceptibility of rats or rabbit fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity data.
- 3) In the absence of complete environmental fate data for difenoconazole and to be protective to infants and children, worst-case fate parameters will be used in the EFED models for ground and surface source drinking water exposure assessments resulting in estimates that are upper-bound concentrations.
- 4) There are currently no registered residential uses for difenoconazole and therefore, non-dietary exposure to infants and children is not expected.

#### 4. Data Gaps

There are no data gaps.

#### 5. Summary of Toxicology Endpoint Selection

The doses and toxicological endpoints selected on difenoconazole for various exposure scenarios are summarized in Table 4.

**Table 4. Summary of Toxicological Endpoints of Difenoconazole**

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary [females 13+]	NOAEL= 25	post-implantation loss, increased resorptions per doe, decreased body weight	developmental rabbit
	UF = 100		
<b>Acute RfD = 0.25 mg/kg</b>			
Acute Dietary (General Population including infants and children)	None	An endpoint attributable to a single exposure (dose) was not available from the oral toxicity studies including the rat and rabbit developmental toxicity studies.	
Chronic Dietary	NOAEL = 0.96	cumulative decreases in body weight gains	chronic/onco rat
	UF = 100	<b>Chronic RfD = 0.01 mg/kg/day</b>	
Short-Term <sup>a</sup> (Dermal)	oral NOAEL=25	post-implantation loss, increased resorptions per dose, decreased body weight	developmental rabbit

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Intermediate-Term <sup>a</sup> (Dermal)	oral NOAEL=1.25	based on decreased pup weight on day 21	2-generation reproduction rat
Long-Term (Dermal) <sup>a</sup> Non Cancer	None	Long-term dermal exposure is not expected based on a one time application as a seed treatment. This risk assessment is not required.	
Long-Term Oral and Dermal <sup>a</sup> (Cancer)	$Q_1^* = 0.157$	Difenoconazole is classified as a Group C, possible human carcinogen with the recommendation of a non-linear (MOE) approach for human risk characterization using the NOAEL of 4.7 mg/kg/d from the males of the mouse oncogenicity study. (CPRC Document, 7/27/94). However, at this time, the Agency has not defined the acceptable level of concern for cancer risk using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the $Q_1^*$ approach. The $Q_1^*$ was determined to be $1.57 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ . This value incorporates the 3/4 scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunsman, 12/8/98).	
Inhalation (Any time period)	None	Based on the low acute toxicity [Toxicity Category IV], the application rate [0.5-1.0 fl.oz./100 lbs of seed] the application method [standard slurry or mist-type seed treater] and the number of applications [1x] there is minimal concern for potential inhalation exposure/risk. This risk assessment is not required for the non-cancer endpoint.	

a =A dermal absorption factor of 75% should be used for route-to-route extrapolation.

## 6. Dietary Exposure and Risk Assessment/Characterization

### a. Dietary Exposure (Food Sources)

#### i. Proposed Uses

##### *Wheat*

Dividend is a flowable concentrate of difenoconazole containing 3 lbs. ai/gal. Dividend is applied as a water-based slurry by mixing with up to 16 oz. water per 100 lbs. seed. Treated seeds are to be dyed in order to distinguish them as being treated. The maximum use rate is 1 fluid oz./100 lbs. seed (10.9 grams or 0.38 oz ai/100 lbs. seed). The label contains the following restrictions: a) do not use treated seed for feed, food or oil; b) green forage may not be grazed until 55 days after planting; c) do not apply to winter barley; d) for use only

by commercial seed treaters (Memo, G. Kramer, D194842, 3/30/94). The data submitted support a 30-day plantback interval for all rotational crops (Memo, G. Kramer, D217119, 9/13/95).

### *Bananas*

Difenoconazole (EPA Reg. No. 100-739) is formulated as Sico 25EC, a emulsifiable concentrate containing 23.9% a.i. A CSF was included for Sico. Sico is currently registered for use on bananas in Belize. Registrations are pending in Central America (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama and the Dominican Republic), Colombia, Ecuador and Mexico. Labels and English translations were provided for all of these regions/countries (Memo, G. Kramer, D216521, 2/23/96).

The maximum use rate is 40.5 g. ai/A (100 g. ai/ha) and a maximum of 12 applications are permitted per year. The minimum re-treatment interval is 18 days. A maximum of 8 applications are recommended when the 18-day re-treatment interval is utilized (Memo, G. Kramer, D216521, 2/23/96).

Difenoconazole can be applied as an emulsion, or in oil only. The emulsion is prepared by mixing 5-10 L oil with 15-20 L water plus 0.5-1.0% emulsifier for each liter of oil. The application volumes are 99-205 l/ha for concentrated applications and 20-25 L/ha for ULV applications. These directions are applicable to both ground and aerial applications. The PHI is 0 days (Memo, G. Kramer, D229926, 10/4/96).

## **ii. Nature of the Residue - Plants**

### *Wheat*

The nature of the residue in wheat is understood. Acceptable metabolism studies using [<sup>14</sup>C]- labeled difenoconazole applied at 1x have been performed in wheat RACs. Difenoconazole was applied in phenyl- and triazole-labeled forms. The major terminal residues in wheat grain were the metabolites triazole and triazole acetic acid; and in wheat straw and forage; triazole alanine, triazole acetic acid and CGA-205375. The parent was not detected in grain and comprised 7-8% of the TRR in forage and 0.3-0.4% of the TRR in straw (Memo, G. Kramer, D203644, 6/16/94).

### *Bananas*

The nature of the residue in plants is believed to be understood. As the nature of the residue is understood in different crops, no metabolism studies for bananas were required.

The residue of concern in bananas is the parent compound only (Memo, G.

Kramer, D216521, 2/23/96).

The nature of the residue is understood in tomatoes, potatoes, wheat (PP#2E4051), and grapes (Memo, G. Kramer, D216521, 2/23/96).

The nature of the residue in **tomatoes** following foliar application is adequately understood. The major terminal residues are the parent compound and its metabolite triazole alanine (CGA-131013) (Memo, R. Lascola, D172067, 10/26/92).

The petitioner has established that the primary metabolic fate of difenoconazole in **potatoes** following foliar application is cleavage of the phenyl-triazole bridge. Triazole-labeling studies indicate that the molecule is metabolized to triazole alanine, while phenyl studies demonstrate conjugating with a number of naturally occurring substrates (Memo, R. Lascola, D172067, 10/26/92).

The nature of the residue in **grapes** is understood. The metabolism of difenoconazole proceeds by hydroxylation of the phenyl ring and/or oxidative cleavage of the dioxolane ring followed by cleavage of the carbon-carbon bridge between the phenyl and triazole rings. Similar results were observed in the wheat, tomato and potato metabolism studies (Memo, G. Kramer, D216521, 2/23/96).

The HED Metabolism Assessment Review Committee (MARC) met on July 14, 1994 to discuss the toxicological significance of potential metabolites. It was decided that none of the difenoconazole metabolites warrant inclusion in the tolerance regulation or separate regulation or inclusion in the dietary risk assessment or additional metabolism or toxicological studies. The triazole metabolites (triazole, triazole alanine, triazole acetic acid) have previously been determined not to be of toxicological concern in conjunction with tebuconazole, a structurally related triazole fungicide. CGA-205375 was determined not to be of concern due to the low potential for residues associated with seed treatment (Memo, G. Kramer, 7/22/94). This conclusion can be expanded to include triazole propanoic acid (Alberto Protzel, Personal Communication 1/17/95) (Memo, Kramer, D210080, 1/18/95). Only the parent compound difenoconazole will be in the tolerance expression.

However, if in the future the registrant wishes to propose tolerances for difenoconazole resulting from foliar uses which result in higher residue levels, then the MARC will reconsider whether CGA-205375 needs to be included in the difenoconazole tolerance expression. If CGA-205375 is included in the tolerance expression, then new analytical enforcement methodology and a second lab validation will be required. If quantifiable levels of residues are found in animal feed items, then animal feeding studies will be required (Memo, G. Kramer, 7/22/94).

### iii. Nature of the Residue - Animals

The nature of the residue in animals is considered understood for the purposes of this petition (2F4107) only (Memo, G. Kramer, D233644, 6/16/94). For any future petition in which there is a greater potential for transfer of residues to meat and milk, additional animal metabolism studies will be required.

The HED MARC met on July 14, 1994 to discuss the toxicological significance of potential metabolites. It was decided that none of the difenoconazole metabolites warrant inclusion in the tolerance regulation or separate regulation or inclusion in the dietary risk assessment or additional metabolism or toxicological studies. The triazole metabolites (triazole, triazole alanine, triazole acetic acid) have previously been determined not to be of toxicological concern in conjunction with tebuconazole. CGA-205375 was determined not to be of concern due to the low potential for residues associated with seed treatment (Memo, G. Kramer, 7/22/94). This conclusion can be expanded to include triazole propanoic acid (Alberto Protzel, Personal Communication 1/17/95) (Memo, Kramer, D210080, 1/18/95).

However, if in the future the registrant wishes to propose tolerances for difenoconazole resulting from foliar uses which result in higher residue levels, the MARC will reconsider whether CGA-205375 needs to be included in the difenoconazole tolerance expression. If CGA-205375 is included in the tolerance expression, then new analytical enforcement methodology and a second lab validation will be required. If quantifiable levels of residues are found in animal feed items, then animal feeding studies will be required (Memo, G. Kramer, 7/22/94).

### iv. Residue Analytical Methods

#### *Plants*

The petitioner proposed Method AG-575B, "Analytical Method for the Determination of CGA-169374 in Wheat Raw Agricultural Commodities by Gas Chromatography with Nitrogen/Phosphorus Detection" as the analytical enforcement method for wheat (Memo, R. Lascola, D172067, 10/22/92) and bananas (Memo, G. Kramer, D216521, 2/23/96).

Frozen samples are homogenized, and residues are extracted by boiling the samples in 8:2 methanol:concentrated ammonium hydroxide solution. The extract is diluted in water and partitioned twice with hexane. The organic layer is then partitioned twice with acetonitrile (ACN). The residues are now in the ACN phase. The ACN is evaporated and redissolved in toluene for cleanup on a silica Sep-Pak column. The toluene is evaporated, the residue dissolved in hexane, and a second cleanup is performed on a phenyl Bond-elut

column. A third cleanup is then performed with a charcoal column, with toluene as the solvent. Detection is achieved by GC with a nitrogen/phosphorus detector. The petitioner notes that it may be necessary to increase the N/P element power in order to obtain sufficient peak height of the lowest calibration standard. A set of 4-6 samples can be extracted, cleaned up, and analyzed in "a 24 hour period." The method does not require use of an untreated commodity or a blank (Memo, R. Lascola, D172067, 10/22/92).

The petitioner submitted a confirmatory method (AG-657, MRID# 440933-01). This method differs from the enforcement method in the GC column and detector used (DB-1701/ECD instead of DB-17/NPD). In bananas fortified at 0.01-0.20 ppm, the average recovery was  $106 \pm 14\%$  with the enforcement method and  $99 \pm 13\%$  with the confirmatory procedure. Conditions for using MSD (monitoring m/z 323 and 265) were also included (Memo, G. Kramer, D229926, 10/4/96).

HED concluded that Method AG-575B is adequate for enforcement purposes. An independent laboratory validation (ILV) of the method has been submitted and a satisfactory petition method validation (PMV) by ACL was completed (Memo, G. Kramer, D194842, 3/30/94).

#### *Animals*

The petitioner proposed Method AG-544A, "Difenoconazole (CGA-169374) Analytical Method for the Determination of CGA-169374 Residues in Dairy and Poultry Tissue, Eggs and Milk by Gas Chromatography," as the analytical enforcement method. The sample is extracted by homogenization for 1 min with 95:5 acetonitrile:concentrated ammonium hydroxide. After filtration, the extract is diluted with water and saturated NaCl and partitioned with hexane. The hexane fraction is partitioned with acetonitrile and the acetonitrile fraction is cleaned-up on a silica gel SepPak. The final extract is analyzed by packed column GC using alkali flame ionization detection (Memo, G. Kramer, D194842, 3/30/94).

HED concludes that Method AG-544A is adequate for enforcement purposes. An ILV of the method was submitted and a satisfactory PMV by ACL was completed (Memo, G. Kramer, D205118, 7/20/94).

#### **v. Multiresidue Methods**

The results of Multiresidue testing of difenoconazole its metabolites, CGA-189138, CGA-205374, and CGA-205375, (MRID# 420900-54) have been forwarded to FDA (Memo, R. Lascola, 5/21/92). The study is entitled "Multiresidue Method Testing of CGA-169374 and Metabolites in Crops and Animal Tissues", CIBA-GEIGY Project No. ABR-89048, by R. K. Williams, CIBA-GEIGY Corporation, Greensboro, NC; 7/20/92; MRID# 420900-54.



Compounds investigated included CGA-169374, CGA-205374, CGA-205375, and CGA-189138. The petitioner concluded that Protocols C, D, and E did not yield sufficient recoveries or responses to be useful for the detection of these chemicals. Protocol A (N-methyl carbamates) does not apply to these chemicals. Protocol B (acids and phenols) only applies to CGA-189138, however recovery of that compound was not tested (Memo, R. Lascola, D172067, 10/22/92).

**vi. Storage Stability Data**

*Wheat*

The petitioner submitted acceptable storage stability data on wheat grain, straw, and forage and in cottonseed, cottonseed oil, and cottonseed meal. The data shows difenoconazole to be stable for up to 24 months frozen storage. HED concludes that storage stability has been demonstrated for the purposes of this petition (Memo, S. Chun, D248285, 10/28/98).

*Bananas*

The results demonstrate that residues of difenoconazole are stable in bananas for up to 12 months of storage. Difenoconazole was previously shown to be stable in potatoes and tomatoes for up to 2 years of storage and in wheat for 1 year (Memos, R. Lascola, D172067, 10/22/92 and G. Kramer, D194842, 3/30/94). Based on submitted studies, storage stability is not an issue for this petition (Memo, G. Kramer, D216521, 2/23/96).

**vii. Crop Field Trials**

*Wheat*

Fifteen field trials were conducted in OK (2), TX (1), NC (1), MT (1), KS (2), CO (1), ND (1), SD (1), AR (1), ID (1), MO (1), MN (1), and NE (1). This corresponds to the following regions: Region 2 (1 trial), Region 4 (1 trial), Region 5 (3 trials), Region 7 (2 trials), Region 8 (6 trials), and Region 9 (2 trials). The number of field trials in each region do not match those suggested in *Residue Chemistry Test Guidelines, OPPTS 860.1500 Crop Field Trials*. A field trial in Region 6, 2 field trials in Region 7, and a field trial in Region 11 are missing; however, the submitted field trials accounted for 83% of total wheat acreage planted. Therefore, no additional field trials in these regions will be required. The wheat field trials were conducted at two application rates, 10.9 g a.i./100 lb. seed (1x) and 21.8 g a.i./100 lb. seed (2x). At each site wheat grain, forage, hay, and straw were collected. Two samples were collected per plot for the 1x application.

The submitted field trial data on wheat RACs are adequate. The average

method recoveries for the field trials were acceptable (> 70%) for wheat RACs. The residue levels of difenoconazole in wheat grain (< 0.01 ppm) and in wheat hay and straw (< 0.05 ppm) were less than the limit of quantitation (LOQ). The LOQ for wheat grain is 0.01 ppm and 0.05 ppm in wheat straw, hay, and forage. Wheat forage had residue levels ranging from < 0.05 ppm - 0.077 ppm. The submitted data indicate that residues of difenoconazole will not exceed the time-limited tolerance for wheat RACs (Memo, S. Chun, D248285, 10/28/98).

### *Bananas*

Nine field trials were conducted in Colombia (3), Honduras (3), and Ecuador (3). Two of three field trials in each country were conducted using an oil emulsion at the single maximum application rate of 100 g a.i./ha (0.22 lb. a.i./ha); one using aerial application and one using ground application. Difenoconazole was applied 8 times for a total maximum application rate of 800 g a.i./ha (1.76 lb. a.i./ha) with a target spray volume range of 20-25 L/ha/application. The third field trial used an oil only formulation at an application rate of 100 g a.i./ha (0.22 lb. a.i./ha) and was also applied 8 times for a maximum application rate of 800 g a.i./ha (1.76 lb. a.i./ha) using aerial application with a target spray volume of 10 L/ha/application. At each site whole banana fruit were collected 0 days after the last application. Specimens were collected from unbagged racemes (bunches) in all field trials. Samples consisted of six fingers (two fingers from top, middle, and bottom hands of a raceme). A total of six replicates were collected (each using another plant raceme) for each treatment. The studies were conducted in accordance with the protocol submitted to and accepted by HED (Memo, G. Kramer, D227491, 8/1/96). The varieties of bananas used in these field trials were: AAA, Cavendish, Robusta, Valery, and Giant Cavendish. The submitted 9 field trial data in bananas are adequate. The residue levels of difenoconazole in whole bananas ranged from <0.02 ppm to 0.13 ppm. The residue levels in banana pulp were all less than the LOQ (0.02 ppm). The residue levels in banana peel ranged from < 0.02 - 0.25 ppm.

An additional six field trials were submitted and reviewed previously (Memos, G. Kramer, D216521 and D229926, 2/23/96 and 10/4/96, respectively). These field trials were conducted in Costa Rica (1 trial), Ecuador (1 trial), Mexico (2 trials), Guatemala (1 trial), and Belize (1 trial). Residue levels in these six field trials ranged from 0.03 -0.16 ppm in whole unbagged bananas and < 0.02 - 0.03 ppm in unbagged banana pulp.

With the submission of 9 field trials and the 6 prior, the field trial data (15 trials) on bananas are adequate. The residue levels of difenoconazole in whole unbagged bananas from all 15 trials ranged from < 0.02 - 0.16 ppm. The residue levels in unbagged banana pulp from all field trials ranged from < 0.02 - 0.03 ppm. The submitted data indicate that residues of difenoconazole

will not exceed the proposed tolerance level of 0.2 ppm for bananas (Memo, S. Chun, D286648, 11/2/98).

**viii. Processed Food/Feed**

*Wheat*

HED previously reviewed a processing study for spring wheat which was seed-treated (2X) and also foliar-treated (10X) 28 days before harvest (Memo, R. Lascola 10/26/92). No residues (<0.01 ppm) were detected in grain or any processed fraction (Memo, G. Kramer, D194842, 3/30/94). No tolerances for the processed commodities are required for wheat.

*Bananas*

There are no processed commodities associated with bananas and therefore no tolerances for processed commodities are required.

**ix. Meat, Milk, Poultry, Eggs**

The registrant has requested (MRID# 428180-06) a waiver for animal feeding studies based on the low potential for residues in feed items and the exaggerated rates used in the animal feeding studies. Based on a diet comprised of 100% wheat RACs and residues at the level of the proposed tolerances, the maximum dietary burden for dairy cattle is estimated to be 0.30 ppm. Two metabolism studies were performed in ruminants (lactating goats) a 10 day study with a dose rate of 4.17 ppm (14X the 0.30 ppm estimated dietary burden) and a 3 day study with a dose rate of 100 ppm (333X the 0.30 ppm estimated dietary burden). The Total Radioactive Residue (TRR) in the goat tissues was used to estimate the expected residues in a feeding study with a dose rate of 0.30 ppm. The maximum residue observed was in liver, estimated to be at a level of 0.02 ppm from both metabolism studies. This value is 2.5X below the LOQ of the proposed analytical enforcement method (0.05 ppm). The estimated residue in milk would be 0.5 ppb, 20X below the method LOQ of 0.1 ppm.

For now, HED is willing to accept the registrants proposal to allow the animal metabolism studies to also serve as feeding studies. Feeding studies in cattle and poultry, as appropriate, will be needed for any future tolerance requested on potential livestock feed commodities which could lead to higher residues of concern in meat, milk and eggs (Memo, G. Kramer, D194842, 3/30/94).

**x. Water, Fish, and Irrigated Crops - Not Applicable**

**xi. Food Handling - Not Applicable**

## xii. Confined Accumulation in Rotational Crops

The nature of the residue is understood. The data indicate that the phenyl/triazole bridge of difenoconazole is cleaved in the soil and that triazole-specific metabolites are preferentially taken up by the rotational crops. The maximum TRR observed with phenyl-labeled difenoconazole was 0.009 ppm (wheat stalks) and with triazole-labeled difenoconazole 0.314 ppm in wheat grain (Memo, G. Kramer, D210080, 1/18/95).

The registrant has submitted the results of two confined crop rotation studies using phenyl-labeled difenoconazole. In the RACs of all rotational crops planted 30-33 days after application of difenoconazole, the TRR was <0.01 ppm. These results support the proposed 30 day plantback restrictions for all rotational crops (Memo, G. Kramer, D217119, 9/13/95).

## xiii. Field Accumulation in Rotational Crops - Not Applicable

## xiv. Tolerance Reassessment Table - Not Applicable

## xv. Anticipated Residues

Anticipated residues were calculated from field trial data (Memo, S. Chun, D253277, 3/11/99).

Table 1. Summary of Difenoconazole Anticipated Residues for Dietary Risk Assessment Calculated

Commodity	Residue Levels to Use in Chronic/Cancer DEEM™ Analysis (ppm)
Bananas	0.01
Plantains	0.01
Wheat grain	0.005
Sweet Corn	0.005
Meat*	0.000014
Meat by-products (except kidney)*	0.00044
Kidney*	0.00012
Fat*	0.000041
Milk	0.000013
Poultry meat	0.000006
Poultry meat by-products (except kidney)	0.000023
Poultry kidney	0.000034
Poultry fat	0.0000030
Eggs	0.000019
Egg whites	0.0000043
Egg yolk	0.000046

\*These anticipated residues should be used for meat, fat and meat by-products of cattle, horses, goats, hogs, and sheep in the DEEM run.

## **xvi. Codex Harmonization**

There are pending Codex MRL's for this compound in Mexico for oats, wheat, and barley. There are MRL's for this compound in Australia for carrots (0.5 ppm), potatoes (0.02 ppm), and bananas (0.5 ppm).

### **b. Dietary Exposure (Drinking Water Source)**

HED and EFED do not have monitoring data available to perform a quantitative drinking water risk assessment for difenoconazole at this time. EFED provided ground and surface water exposure estimates for use of difenoconazole (parent compound only).

Since GENEEC and SCI-GROW are not designed to estimate runoff or leaching for seed treatment pesticides, there are uncertainties in the predictive potential of the Tier 1 modeling. Additional uncertainties are associated with the use of unreviewed "screened" environmental fate data. It was necessary to use screened environmental fate data in the assessment because there was insufficient time to conduct a formal data review before the Registration Division (RD) due date. The noted uncertainties in the water assessment, however, are not expected to substantially decrease the conservativeness of the Tier 1 modeling results (Memo, J. Hetrick, 2/9/99).

The main uncertainty in the Tier 1 FQPA water assessment is the use of GENEEC and SCI-GROW models to estimate runoff and leaching of difenconazole from seed treatment use. These models do not account for the pesticide absorption to the seed coat. For purposes of this assessment, it is assumed that difenoconazole does not absorb to the seed coat and hence is simulating a broadcast applied pesticide. This assumption is expected to provide a conservative leaching and runoff scenario (Memo, J. Hetrick, 2/9/99).

Another uncertainty in the water assessment is the use of unreviewed environmental fate data; the photo degradation in water study (MRID 42245128), batch equilibrium study (MRID 42245135 and 42245136), and aerobic soil metabolism study (MRID 42245131) were screened for acceptability of Subdivision N guidelines. The studies will be reviewed formally at a later date. EFED notes that interpretation of Tier 1 modeling results is not likely to be altered through the formal data evaluation process because of the conservativeness in the input parameter selection (Memo, J. Hetrick, 2/9/99).

Other uncertainties in the model assessments are associated with the application rate of difenconazole. The maximum seeding rate for wheat (120 lbs wheat seed/A) was used to calculate the maximum difenconazole application rate. EFED notes that the planting rates for wheat can range from 60 to 120 lbs seed/A (Memo, J. Hetrick, 2/9/99).

### **i. Surface Water Estimates**

Surface water estimates were made using the GENEEC model and available fate data for difenoconazole. EFED calculated the following Tier 1 Estimated Environmental Concentrations (EECs) for difenoconazole in surface water:

Acute or peak EECs: 0.125 ppb  
Chronic (56-day) EECs: 0.048 ppb

Note: According to OPP drinking water guidance (HED SOP 98.4), the 90/56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment would be **0.016 ppb**.

### **ii. Ground Water Estimates**

Using the SCI-GROW (Screening Concentration In Ground Water) model to estimate concentrations in ground water for the parent, the following EEC was calculated:

Difenoconazole: 0.00084 ppb

These concentrations can be considered as both the acute and chronic values.

### **iii. Input Data and Assumptions for Models**

#### *Surface Water*

GENEEC is a single event model (one runoff event), but can account for spray drift from multiple applications. GENEEC is hardwired to represent a 10 ha field immediately adjacent to a 1 ha pond, 2 m deep with no outlet. The pond receives a spray drift event from each application plus one runoff event, which moves a maximum of 10% of the applied pesticide into the pond. This runoff can be reduced by degradative processes in the field and by the effects of binding to soil in the field. In the GENEEC model, spray drift is equal to 1% of the applied for ground spray application and 5% for aerial application.

GENEEC does have certain limitations and is not an ideal tool for use in drinking water risk assessments. Surface-water-source drinking water tends to come from bodies of water that are substantially larger than a 1 hectare pond. Furthermore, GENEEC assumes that essentially the whole basin receives an application of the chemical. In virtually all cases, basins large enough to support a drinking water facility will contain a substantial fraction

of area which does not receive the chemical. Furthermore, the persistence of the chemical near the drinking water facility is usually overestimated because there is always at least some flow in a river or turn over in a reservoir or lake.

Although GENEEC does have these limitations, it can be used in screening calculations and does provide an upper bound on the concentration of pesticide that can be found in drinking water. If a risk assessment based on GENEEC does not exceed the level of concern, then the actual risk is not likely to be exceeded. However, since GENEEC can substantially overestimate true drinking water concentrations, it will be necessary to refine the GENEEC estimate when the level of concern is exceeded. In those situations where the level of concern is exceeded and the GENEEC value is a substantial part of the total exposure, EFED can use a variety of methods to refine the exposure estimates.

The application rate of difenconazole is based on a seed treatment rate of 0.025 lbs a.i./100 lbs (EPA Reg. No. 100-778) and of maximum seeding rate 120 lbs seed/A. Therefore, the maximum difenconazole application rate is 0.03 lbs ai/A. Based on a preliminary screen of the environmental fate data, difenconazole is expected to be relatively immobile and persistent in terrestrial environments. The adsorption coefficient for difenconazole is 12.76 mL/g ( $K_{oc}=3866$ ) in an agricultural sand, 62.97 mL/g ( $K_{oc}= 3470$ ) in sandy loam soil, 54.84 mL/g ( $K_{oc}=7734$ ) in silt loam soil, and 47.18 mL/g ( $K_{oc}=7,734$ ) in a silty clay loam soil. The aerobic soil metabolism half-life for difenconazole ranged from 175 to 1600 days. Difenconazole had a first-order photo degradation in water half-life of 5.68 days. The estimated maximum concentration of difenoconazole in surface water following application to non-crop areas is **0.125 ppb** and the 56-day average concentration is **0.048 ppb** (Memo, J. Hetrick, 2/9/99).

#### *Ground Water*

SCI-GROW is an empirical screening model based on actual ground water monitoring data collected from small-scale prospective ground water monitoring studies for the registration of a number of pesticides that serve as benchmarks for the model. The current version of SCI-GROW provides realistic estimates of pesticide concentrations in shallow, highly vulnerable ground water (i.e., sites with sandy soils and depth to ground water of 10 to 20 feet). There may be exceptional circumstances under which concentrations of a pesticide may exceed the SCI-GROW estimates; however, such exceptions should be rare since the SCI-GROW model is based exclusively on ground water concentrations resulting from studies conducted at sites (shallow ground water and coarse soils) and under conditions (high irrigation) most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW are based on the largest 90-day average concentration recorded during the sampling period. Because of the

conservative nature of the monitoring data on which the model is based, SCI-GROW provides an upper bound estimate of pesticide residues in water. Because of the belief that pesticide concentrations in ground water do not fluctuate widely, SCI-GROW provides one concentration estimate to be used as a maximum and an average pesticide concentration value in ground water.

The application rate of difenconazole is based on a seed treatment rate of 0.025 lbs a.i./100 lbs (EPA Reg. No. 100-778) and of maximum seeding rate 120 lbs/A. Therefore, the maximum difenconazole application rate is 0.03 lbs ai/A. Based on a preliminary screen of the environmental fate data, difenconazole is expected to be relatively immobile and persistent in terrestrial environments. The adsorption coefficient for difenconazole is 12.76 mL/g ( $K_{oc}=3866$ ) in an agricultural sand, 62.97 mL/g ( $K_{oc}= 3470$ ) in sandy loam soil, 54.84 mL/g ( $K_{oc}=7734$ ) in silt loam soil, and 47.18 mL/g ( $K_{oc}=7,734$ ) in a silty clay loam soil. The aerobic soil metabolism half-life for difenconazole ranged from 175 to 1600 days. Difenconazole had a first-order photo degradation in water half-life of 5.68 days. The concentration estimated in ground water is **0.00084 ppb**. (Memo, J. Hetrick, 2/9/99).

**c. Dietary Risk Assessment and Characterization**

**i. Chronic Risk (TMRC)**

A chronic dietary risk assessment was required for difenoconazole. The RfD used for the chronic dietary analysis for difenoconazole is **0.01 mg/kg bwt/day**.

Chronic dietary exposure estimates for difenoconazole are summarized in Attachment 1 (analysis dated 3/1/99). The chronic DEEM™ dietary exposure analysis used mean consumption (3-day average). Anticipated residues and % CT information for select commodities were used. The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity.

The FQPA Safety Factor was reduced to 1x. Therefore the chronic PAD and the chronic RfD are the same. The Agency's level of concern for chronic dietary risk is exceeded if the exposure utilizes more than 100% of the RfD. Dietary exposures for the U.S. general population and other highly exposed subgroups are presented in Table 5. The other subgroups included in Table 5 represent all children subgroups and the highest dietary exposures for their respective subgroups (i.e., females and the other general population subgroup higher than U.S. population).



Table 5. Chronic DEEM™ Results Using Mean Consumption Data- Difenconazole

Subgroups	Exposure (mg/kg/day)	% RfD
U.S. Population (48 states)	0.000005	< 1
Non-Hispanic other than black or white	0.000006	< 1
All infants (< 1 year)	0.000016	< 1
Nursing Infants (< 1 year old)	0.000007	< 1
Non-Nursing Infants (< 1 year old)	0.000019	< 1
Children (1-6 years old)	0.000011	< 1
Children (7-12 years old)	0.000005	< 1
Females (13+/-nursing)	0.000006	< 1
Seniors (55+)	0.000006	< 1

The chronic dietary risk does not exceed the Agency's level of concern.

## ii. Carcinogenic Risk

The CPRC classified difenconazole as a **possible human carcinogen** (Memo, Jess Rowland and Esther Rinde, 7/27/94). This chemical would now be classified as a "likely human carcinogen" in accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996).

The Committee recommended that a non-linear approach (MOE) for human risk characterization and extrapolation of risk be conducted using the NOAEL from the 2-year mouse study. Using the NOAEL of 4.7 mg/kg/day determined by the HED CPRC, the dietary cancer MOE was determined to be **8400** for the U.S. population. At this time, the Agency has not defined the acceptable level of concern for cancer risk using the MOE approach.

Therefore, the linear  $Q_1^*$  approach was used for calculating cancer risk. A  $Q_1^*$  of  $0.157 \text{ (mg/kg/day)}^{-1}$  was determined, based on the male mouse liver adenoma and/or carcinoma combined tumor rates (Memo, Lori Brunsman, 12/8/98).

The dietary exposure analysis estimating potential cancer risks for difenconazole are summarized in Attachment 1 (analysis dated 3/1/99). The analysis was performed using ARs and % CT information for select commodities to estimate the Excess Lifetime Dietary Cancer Risk for the general population. The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. The DEEM™ analysis used mean consumption, assumes a 70 year lifetime exposure, and gave the

following results:

Subgroups	Dietary Exposure (mg/kg/day)	Excess Lifetime Dietary Cancer Risk
U.S. Population (48 states)	0.000005	$8.4 \times 10^{-7}$

The cancer dietary risk does not exceed the HED's level of concern.

### iii. Acute Dietary Risk

An acute dietary risk assessment is required for difenoconazole. The acute NOAEL of 25 mg/kg/day based on in utero post-implantation loss and resorptions/doe and a significant decrease in fetal weight at 75 mg/kg/day during days 7 and 19 of gestation. The acute RfD is 0.25 mg/kg/day. HED's detailed acute analysis estimated the distribution of single-day exposures for females (13+ years old). A dose and endpoint were not selected for the general U.S. population and infants and children because there were no in utero effects observed in oral toxicological studies including maternal toxicity in the developmental toxicity studies in rats or rabbits that could be attributable to a single dose (exposure) (Memo, A. Kocialski and Jess Rowland, 9/25/98). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 CSFII and accumulated exposure to the chemical for each commodity. Each analysis assumes uniform distribution of difenoconazole in the commodity supply.

The acute exposure analysis was performed using tolerance level residues and assumed 100 percent crop treated (Attachment 1). The FQPA Safety Factor was reduced to 1x. Therefore the acute PAD and the acute RfD are the same. For acute dietary risk, the Agency's level of concern is for estimated exposure greater than 100% of the RfD. Totals from the proposed new and published uses at the 95<sup>th</sup> percentile of exposure are listed in Table 6.

**Table 6. Acute Dietary Exposure Results**

Subgroups	Exposure (mg/kg/day)	% RfD
Females (13+/pregnant/not nursing)	0.000913	<1
Females (13+/nursing)	0.001079	<1
Females(13-19 yrs/not preg. or nursing)	0.000941	<1
Females (20+ years/not preg. or nursing)	0.000804	<1
Females (13-50 years)	0.000869	<1

The acute dietary risk does not exceed the Agency's level of concern.

#### iv. Drinking Water Risk (Acute, Chronic, and Cancer)

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs. The Agency uses DWLOCs internally in the risk assessment process as a surrogate measure of potential pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

OPP has calculated a DWLOC for acute exposure to difenoconazole in surface and ground water for females (13+ years old, nursing) to be **7500 ppb**. For chronic (non-cancer) exposure to difenoconazole in surface and ground water, the DWLOCs are **350** and **100 ppb** for the U.S. population and nursing infants (<1 year old), respectively. For chronic (cancer) exposure to difenoconazole in surface and ground water, the DWLOC is **0.048 ppb** for the U.S. population. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEM™ analysis) was subtracted from the acute RfD to obtain the acceptable acute exposure to difenonconazole in drinking water. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from the DEEM™ analysis) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to difenonconazole in drinking water. To calculate the DWLOC for chronic exposures relative to a carcinogenic toxicity endpoint, the chronic (cancer) dietary food exposure (from the DEEM™ analysis) was subtracted from the ratio of the negligible cancer risk to the  $Q_1^*$  to obtain the acceptable chronic (cancer) exposure to difenonconazole in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures. The 2 liters (L) of drinking water consumed per day by adults and the 1 L per day consumed by children are default assumptions. The Agency's default body weights are: males - 70kg, females - 60kg, and children - 10 kg. Tables 7, 8, and 9 summarize the dietary and water exposure for chronic, acute, and cancer.

$$DWLOC (\mu\text{g/L}) = \frac{\text{water exposure (mg/kg/day)} \times (\text{body weight})}{\text{consumption (L)} \times 10^{-3} \text{ mg}/\mu\text{g}}$$

**Table 7. Chronic Scenario for Drinking Water**

Subpopulation	Food Exposure (from DEEM™ in mg/kg/day)	Maximum Water Exposure <sup>1</sup> (mg/kg/day)	RfD mg/kg/day	SCI-GROW <sup>2</sup> (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. Population	0.000005	0.01	0.01	0.00084	0.016	350
Females (13+ yrs/nursing)	0.000006	0.01	0.01	0.00084	0.016	300
Non-Nursing Infants (<1 year old)	0.000019	0.01	0.01	0.00084	0.016	100

<sup>1</sup> Maximum Water Exposure(mg/kg/day) = RfD (mg/kg/day) - dietary exposure from DEEM™ (mg/kg/day).

<sup>2</sup> The highest application rate was used.

U.S. Population: DWLOC = 350 ppb

$$DWLOC (ppb) = \frac{0.0100 \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ L} \times 10^{-3} \text{ mg/}\mu\text{g}} = 350 \text{ ppb}$$

Females (13+ yrs, nursing): DWLOC = 300 ppb

$$DWLOC (ppb) = \frac{0.00999 \text{ mg/kg/day} \times 60 \text{ kg}}{2 \text{ L} \times 10^{-3} \text{ mg/}\mu\text{g}} = 300 \text{ ppb}$$

Nursing Infants(<1 yr): DWLOC = 100 ppb

$$DWLOC (ppb) = \frac{0.00998 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \text{ L} \times 10^{-3} \text{ mg/}\mu\text{g}} = 100 \text{ ppb}$$

**Table 8. Acute Scenario for Drinking Water**

Subgroup	RfD (mg/kg/day)	NOAEL (mg/kg/day)	Food Exposure (from DEEM™) (mg/kg/day)	Water Exposure (mg/kg)	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
Females (13+, nursing)	0.25	25	0.001079	0.25	0.00084	0.125	7500

Females (13+ yrs, nursing): DWLOC = 7500 ppb

$$DWLOC (ppb) = \frac{0.249 \text{ mg/kg/day} \times 60 \text{ kg}}{2 \text{ L} \times 10^{-3} \text{ mg/}\mu\text{g}} = 7500 \text{ ppb}$$

**Table 9. Cancer Scenario for Drinking Water**

Subgroup	RfD (mg/kg/day)	Q <sub>1</sub> <sup>*</sup> (mg/kg/day) <sup>-1</sup>	Food Exposure (from DEEM™) (mg/kg/day)	Water Exposure (mg/kg)	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. population	0.01	0.157	0.000005	0.000001	0.00084	0.016	0.048

U.S. population: DWLOC = **0.048 ppb**

$$\begin{aligned} \text{Allowable Exposure} &= \frac{1 \times 10^{-6}}{Q_1} \\ &= \frac{1 \times 10^{-6}}{0.157} = 6.4 \times 10^{-6} \text{ mg/kg/day} \end{aligned}$$

$$\text{DWLOC (ppb)} = \frac{0.00000137 \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ L} \times 10^{-3} \text{ mg}/\mu\text{g}} = 0.048 \text{ ppb}$$

Estimated maximum concentrations of acute and chronic exposure to difenoconazole in surface water are **0.125 ppb** and **0.016 ppb**, respectively. Estimated average concentration of difenoconazole in ground water is **0.00084 ppb**. (*Note: For the purposes of the screening-level assessment, the maximum and average concentrations in ground water are not believed to vary significantly*). The GENEEC model estimated maximum concentration is compared directly to the DWLOC for acute exposure. The maximum estimated concentrations of difenoconazole in surface water are less than OPP's DWLOCs for difenoconazole in drinking water as a contribution to acute, chronic, and cancer aggregate exposure. Therefore, taking into account the uses proposed in this action, OPP concludes with reasonable certainty that residues of difenoconazole in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in levels of aggregate human health exposure and risk of concern at this time.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to back-calculated "levels of comparison" for difenoconazole in drinking water. These DWLOCs in drinking water were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of difenoconazole in surface waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate risk assessment process.

d. **Statement of the adequacy of the dietary exposure database to assess infants' and children's exposure**

The dietary (food and water) exposure database for difenoconazole is adequate to assess infants' and children's exposure for the proposed uses.

## **7. Occupational/Residential Exposure and Risk Assessment/Characterization**

Novartis currently has several registered labels for different formulations of Dividend. These include Dividend (EPA reg.# 100-739), Dividend (100-740), Dividend 0.15 FS (EPA reg.# 100-777), Dividend 0.31 FS (EPA reg.# 100-778), Dividend MG (EPA reg.# 100-779), Dividend WS (EPA reg.# 100-814), Dividend XL (EPA reg.# 100-885), and Dividend XL RTA (EPA reg.# 100-885). Dividend (EPA reg.# 100-739) and Dividend MG (EPA reg.# 100-779) are technical products, formulated into end-use products. Dividend XL and XL RTA are mixtures of difenoconazole with other fungicides. Some of these labels indicate special formulation for on-farm use (EPA reg.#s 100-777, 100-778, 100-885). None of the labels have uses that could result in residential exposures.

There are two products for this petition, one for wheat seed (EPA reg. # 100-740) and one for the technical product (EPA reg. # 100-739). The label for Dividend™ (EPA reg.# 100-740) is strictly for commercial seed treatment and contains the highest amount of active ingredient applied. Therefore, this label was used to develop the occupational exposure estimates.

### **a. Occupational and Residential Exposure**

#### **i. Summary of Use Patterns and Formulations**

This occupational exposure assessment addresses the use of Dividend™ (EPA reg. # 100-740), the 32.8% liquid formulation of difenoconazole on wheat. Difenoconazole is a fungicide used as a systemic seed dressing to control certain seed-borne and soil-borne diseases. It is applied as a water-based slurry using standard slurry or mist-type commercial seed treaters. The product label specifies an application rate of 0.024 pounds active ingredient (a.i.) per 100 pounds of seed.

Difenoconazole is not currently registered for any residential uses. Therefore, no non-dietary, non-occupational exposure is anticipated.

#### **ii. Seed Treatment Exposures and Assumptions**

In a typical seed treatment facility, (according to Mr. Brad Russell of the Novartis Seed Treatment Facility (oral personal communication with Olga Odiott, 10/98)), treatment is usually done using automatic and computerized equipment. In the case of difenoconazole, due to the small amount usually used, the fungicide is added manually (via graduated cylinder) to the treatment tank. In addition, seed treater, baggers and sewers are also part of the operation. The work area is supplied with aspirators to minimize any potential inhalation exposure. For difenoconazole, this activity is usually performed 5 days a week for 2 to 3 weeks, 3 times per year. HED's exposure assessment is based on the assumptions in Table 10.

**Table 10. Assumptions for Commercial Handler Exposure Assessments**

Factors	Quantities/Units		Source
Worker involved in commercial seed treatment	mixer/operator, bagger, bag sewer		Study: Worker Exposure to Apron Flowable While Treating Seed Commercially
Bag size	50 lbs.		
Bags produced per hour	250		
Hours worked per day	8		
Personal Protective Equipment worn by Mixer, Bagger and Bag Sewer	Chemical apron, goggles, gloves for mixer only and long-sleeved-shirt and pants for bagger and sewer.		Study: Worker Exposure to Apron Flowable While Treating Seed Commercially
Mixer unit exposures (mg/kg ai handled)	Dermal: 0.0610	Inhalation: 0.000775	PHED version 1.1
Bag sewer unit exposures (mg/kg ai handled)	Dermal: 0.0346	Inhalation: 0.0056	
Bagger unit exposures (mg/kg ai handled)	Dermal: 0.0182	Inhalation: 0.000518	
Application rate	0.024 lb ai/100 lbs seed		label
Application Type	commercial mist-type seed treatment equipment		
Days worked per week	5		Mr. Brad Russell, Novartis Seed Treatment Facility
Days worked per year	45		

HED has very limited data for seed treatment scenarios. These exposure estimates for commercial seed treaters are based on data from a study entitled **Worker exposure to Apron Flowable while treating seed commercially** (Ciba-Geigy, 1993) submitted in support of MAXIM 4FS. This study was reviewed by HED in August of 1994 (Memo, B. Kitchens, 9/23/94).

This study determined the amount of active ingredient that mixer/operators, baggers and bag sewers were exposed to during the commercial treatment of seed. Both the study and the wheat use are for a liquid flowable formulation and employ the use of a mist-type applicator. The study was considered supplemental but upgradable by HED, pending the registrant's response to questions concerning field recoveries and ambient conditions. However, the study is the best body of data available for commercial seed treatment

operations. HED notes that although limited, data from the open literature suggests that overall, pesticide application of seed treatment in commercial environments is a relatively safe operation, with low expected exposures (Bulletin of Environ. Contam. Toxicol. 31, 244-250, Grey, Marthre and Rogers, 1983).

### iii. Commercial Seed Treater Exposure Assessment

Lifetime Average Daily Dose (LADD) calculation for commercial seed treaters were done assuming 5 days worked per week for 3 weeks, 3 times each year (oral personal communication from Mr. Russell of Novartis Seed Treatment Facility to Olga Odiott, 10/98, written confirmation to follow). Further, the LADD calculation assumes that the individual would work 35 out of 70 years.

Based on use patterns, only short- and intermediate-term dermal exposures are expected. Both the short- and intermediate-term MOEs were greater than 100 and therefore, below HED's level of concern. Although an inhalation endpoint (any time-period) was not selected for difenoconazole, for purposes of the cancer risk calculations, inhalation exposures were estimated and added to the dermal exposures. The CPRC committee determined that an MOE approach was appropriate to determine cancer risk. However, at this time, the Agency has not defined the level of concern for cancer using the MOE approach. Therefore, the  $Q_1^*$  approach was used for calculating cancer risk. A  $Q_1^*$  of 0.157 was determined, based on the male mouse liver adenoma and/or carcinoma combined tumor rates (memo, Lori Brunsman, 12/8/98). The highest estimated cancer risk for the commercial seed treater was determined to be  $8.2 \times 10^{-5}$  for the mixer/operator. Generally, HED's level of concern for occupational exposure is for cancer risk greater than  $1 \times 10^{-4}$ . Therefore, the cancer risk for commercial seed treatment does not exceed HED's level of concern. Table 11 summarizes the HED/RAB1 estimates for exposure for commercial seed treaters including mixer/loaders, baggers and bag sewers.



**Table 11. Seed Treatment Exposure to Dividend™ fungicide\***

Job Function	Dermal Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Inhalation Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Short-Term Dermal MOE	Intermediate-Term Dermal MOE	Lifetime Average Daily Dose (LADD) mg ai/kg bw/day	Cancer MOE	Cancer Risk (Q*)
Mixer/Operator	0.0083	0.00014	$3.0 \times 10^3$	$1.5 \times 10^2$	0.00052	$9.0 \times 10^3$	$8.2 \times 10^{-5}$
Bag Sewers	0.0047	0.0010	$5.3 \times 10^3$	$2.6 \times 10^2$	0.00035	$1.3 \times 10^5$	$5.6 \times 10^{-5}$
Bagger	0.0025	0.000094	$1.0 \times 10^4$	$5.0 \times 10^2$	0.00016	$3.0 \times 10^4$	$2.5 \times 10^{-5}$

The following equations were used to determine the expected worker exposures resulting from the commercial seed treatment applications of difenoconazole on wheat.

$$\text{MOE short-term dermal} = \frac{\text{NOAEL}(25 \text{ MG / KG / DAY})}{\text{ADD}} \quad \text{MOE intermediate-term dermal} = \frac{\text{NOAEL}(1.25 \text{ MG / KG / DAY})}{\text{ADD}}$$

$$\text{ADD} = \left( \left( \text{UNIT EXPOSURE} \left( \frac{\text{MG}}{\text{KG AI}} \right) \right) \times \left( \frac{1 \text{ KG}}{2.2 \text{ LBS}} \right) \times \left( \text{APPLICATION RATE} \left( \frac{\text{LBS AI}}{100 \text{ LBS SEED}} \right) \right) \right) \times 0.75(\text{dermal absorption})$$

$$\left( \frac{\text{SEED}}{\text{BAG}} \right) \times \left( \frac{\text{BAGS}}{\text{HOUR}} \right) \times \left( \frac{\text{HOURS}}{\text{DAY}} \right) \times \left( \frac{1}{\text{BODY WIEGHT}(60 \text{ KG})} \right)$$

$$\text{LADD} = \text{ADD inhalation \& dermal} \times \left( \frac{\text{Days Worked per Year}}{\text{Total Days per Years}} \right) \times \left( \frac{35 \text{ Years Worked}}{70 \text{ Year Lifetime}} \right)$$

$$\text{CANCER RISK} = Q^* (0.157 \text{ mg / kg / day}) \times \text{LADD}$$

#### iv. Farm Worker Exposures and Assumptions

Since wheat is planted mechanically, the potential agricultural worker exposures to difenoconazole are expected to be minimal. Wheat planting usually consists of two functions; mixer/loader and driver/planter. The highest amount of exposure is expected for the mixer/loader scenario, opening the treated seed bags and emptying the contents into the application equipment. The driver/planter is not expected to receive significant exposure.

PHED data was used to estimate exposure to workers. Currently, PHED does not contain data on this specific scenario. Therefore, the closest possible match is GRANULAR OPEN MIXING. The 'no gloves' unit exposure was used as a conservative assumption. The quality of the dermal data is considered 'low confidence' (ABC grade, low replicates, and poor grade quality of hand replicates). The quality of the inhalation data is considered 'high confidence' (AB grade, high replicates) (PHED v 1.1 Surrogate Table).

Typical wheat planting-practice information, such as the number of acres that are planted per day and the pounds of seed planted per acre were obtained from the Texas Department of Agriculture (oral personal communication from Mr. Trostle to Olga Odiott, 10/98). The information considered in calculating exposure estimates is listed in Table 12.

**Table 12: Mixer/Loader Exposure Assumptions**

Scenario	Exposure	Unit Exposure (mg/lb ai)	Application Rate	Pounds seed /Acre	Acres/day <sup>1</sup>	Body Weight (kg)
Mixer/Loader	Dermal	0.0084	0.024 lbs ai/100 lbs seed	75	1000	60
Mixer/Loader	Inhalation	0.0017	0.024 lbs ai/100 lbs seed	75	1000	60
<u>Source</u>	- -	PHED 1.1 Surrogate Table. Granular open pour, no gloves	Label	TX Dept. of Agriculture	TX Dept. of Agriculture	Default value

<sup>1</sup> This information was based on the average amount of acres planted with wheat divided by the number of farms growing wheat. The relevant data have been taken from the 1992 Census of Agriculture.

#### v. Farm Worker Exposure Assessment

In calculating LADD, it was assumed that the farm worker would plant approximately 1000 acres per day, 3 days per week for 2 weeks each year, for 35 years over a 70-year lifespan. Table 13 lists Mixer/Loader exposure estimates.

Long-Term calculations were not performed due to a maximum of 6 days of exposure per year. Short- and Intermediate-Term calculations (7 days to several months) were performed to assess the worker exposure for the scenario with the highest exposure. Both the short- and intermediate-term MOEs were greater than 100 and therefore, below HED's level of concern. The cancer calculation (using the Q<sub>1</sub>\* approach) for the highest exposed worker (mixer/loader) was determined to be 3.1 x 10<sup>-6</sup>. Therefore, the cancer risk for all farm workers handling seeds treated with difenoconazole is below HED's level of concern.

*Exposure estimates were only done for the mixer/loader scenario, representing the highest possible exposure for all workers performing planting of treated seeds.*

**Table 13. Mixer/Loader Exposure to Dividend™ Treated Seeds**

Job Function	Dermal Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Inhalation Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Short-Term Dermal MOE	Intermediate-Term Dermal MOE	LADD mg ai/kg bw/day	Cancer MOE	Cancer Risk (Q*)
Mixer/Loader	0.0019	0.00051	1.3 x 10 <sup>4</sup>	6.6 x 10 <sup>2</sup>	0.000020	4.8 x 10 <sup>5</sup>	3.1 x 10 <sup>-6</sup>

The following equations were used to determine the expected worker exposures resulting from the opening and loading of bags of wheat seed treated with difenoconazole.

$$\text{MOE short-term dermal} = \frac{\text{NOAEL}(25 \text{ MG / KG / DAY})}{\text{ADD}} \quad \text{MOE intermediate-term dermal} = \frac{\text{NOAEL}(1.25 \text{ MG / KG / DAY})}{\text{ADD}}$$

$$\text{MIXER / LOADER: ADD} = \left( \left( \left( \text{UNIT EXPOSURE} \left( \frac{\text{MG}}{\text{LB AI}} \right) \right) \times \left( \text{APPLICATION RATE} \left( \frac{\text{LBS AI}}{100 \text{ LBS SEED}} \right) \right) \right) \right) \times 0.75 \text{ (dermal absorption)}$$

$$\times \left( \frac{\text{LBS SEED}}{\text{ACRE}} \right) \times \left( \frac{\text{ACRES}}{\text{DAY}} \right) \times \left( \frac{1}{\text{BODY WIEGHT (60 kg)}} \right)$$

$$\text{LADD} = \text{ADD inhalation \& dermal} \times \left( \frac{\text{Days Worked per Year}}{\text{Total Days per Year}} \right) \times \left( \frac{35 \text{ Years Worked}}{70 \text{ Year Lifetime}} \right)$$

$$\text{CANCER RISK} = \text{Q}^* (0.157 \text{ mg / kg / day}) \times \text{LADD}$$

**vi. Post-Application Exposures and Assumptions**

**a). Occupational**

There is no post-application exposure expected as a result of the commercial seed treatment use of difenoconazole.

**b). Residential**

There are currently no residential uses for difenoconazole.

**b. Occupational and Residential Risk Assessment/Characterization**

**i. Risks from Dermal, and Inhalation Exposures for Seed Treaters**

Although there are uncertainties about the quality of the data, HED concludes that the potential risk will not exceed the levels of concern. HED's level of concern for short and intermediate exposure difenoconazole are for MOEs below 100. Estimated short- and intermediate-term dermal MOEs are well above 100. The exposure assessment is based on the best body of data that is available to HED at this time. HED notes that although limited, data from the open literature suggests that overall, pesticide application of seed treatment in commercial environments is a relatively safe operation, with low expected exposures (Bulletin of Environ. Contam. Toxicol. 31, 244-250,

Grey, Marthre and Rogers, 1983).

The cancer risk for commercial seed treaters was determined to be  $8.2 \times 10^{-5}$  for the worst-case scenario. Therefore, the cancer risk for commercial seed treaters does not exceed HED's level of concern (generally below  $1 \times 10^{-4}$  for non-dietary exposure).

**ii. Risks from Dermal, and Inhalation Exposures for Farm Workers**

Estimated MOE's are well above 100, and therefore below HED's level of concern. Because planting of wheat is done mechanically, the mixer/loader scenario represents the highest exposure activities for farm workers. Therefore, exposure estimates were only done for this group of farm workers. Using the  $Q_1^*$  approach, the cancer risk for farm workers was determined to be  $3.1 \times 10^{-6}$  for the worst-case scenario. Therefore, the cancer risk for farm workers does not exceed HED's level of concern ( $1 \times 10^{-4}$  for non-dietary exposure).

**iii. Risk from Residential Exposure**

There are no residential uses for difenoconazole at this time.

**iv. Risk from Post-Application Exposure**

There are no post-application exposures related to this use of difenoconazole. For this use, It is strictly a commercial seed treatment product.

**v. Incident Reports**

Incident report data are available for difenoconazole. Two cases have been reported in OPP's Incident Data System by the registrant. They consist of instances of human exposure (in Ohio and Minnesota) which both took place in 1995. Neither case was confirmed and it is not known whether the alleged cases sought medical attention for their symptoms. One report (that was not wearing protective clothing) includes complaints of pain and tingling in the arms and blurred vision. The second includes complaints of primarily of flu-like symptoms and redness of the hands. There were no reports of exposure or illness due to difenoconazole from 1993 to 1996 among 431,684 unintentional cases reported to the nation's poison control centers participating in the Toxic Exposure Surveillance System. The California Pesticide Illness Surveillance Program had no reports of difenoconazole-related illness from 1982 through 1995. Based on lack of incidents from these three sources, no changes in labeling are recommended.

**c. Statement of the adequacy of the residential exposure data base to assess infants' and children's exposures**

No risk assessment was performed because there are no residential uses for this product.

**8. Aggregate Exposure and Risk Assessment/Characterization**

There are no proposed or existing residential uses for difenoconazole and occupational uses of difenoconazole will not result in post-application residential exposure.

Therefore, aggregate exposure risk assessment have been limited to food and water only. Details concerning the assumptions used in deriving exposure estimates and risk characterizations were discussed previously in this document.

**a. Acute Aggregate Exposure and Risk**

From the acute dietary (food only) risk assessment, a high-end exposure estimate was calculated for the subgroup, females 13+ years old. For females 13+ years old, less than 1% of the RfD is occupied by dietary exposure (food only). The acute dietary exposure for females 13+ years old is below HED's level of concern.

An acute RfD was not established for the general population including infants and children because there were no effects observed in oral toxicity studies including maternal toxicity in the developmental toxicity studies in rats and rabbits attributable to a single exposure (Memo, A. Kocialski and Jess Rowland, 9/25/98).

The maximum estimated concentrations of difenoconazole in surface and ground water are less than OPP's DWLOCs for difenoconazole as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of difenoconazole in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate acute risk assessment process.

**b. Short- and Intermediate-Term Aggregate Exposure and Risk**

Since no registered residential uses or exposure scenarios were identified for short- and intermediate-term exposure scenarios, short- and intermediate-term aggregate risk assessments are not required (Memo, A. Kocialski and Jess Rowland, 9/25/98).

**c. Chronic Aggregate Exposure and Risk**

Chronic risk estimates associated with exposure to difenoconazole in food and water do not exceed OPP's level of concern. The chronic DEEM™ dietary exposure analysis used mean consumption (3-day average). Anticipated residues and % CT information for select commodities were used to estimate dietary exposure for the general population and 28 subgroups. HED has concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of difenoconazole is less than 1% for the RfD for all populations. The estimated average concentrations of difenoconazole in surface and ground water are less than OPP's DWLOCs for difenoconazole as a contribution to chronic aggregate exposure. Therefore, OPP concludes with reasonable certainty, that residues of difenoconazole in drinking water do not contribute significantly to the aggregate chronic human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate chronic risk assessment process.

**d. Cancer Aggregate Exposure and Risk**

The DEEM™ cancer dietary exposure analysis used anticipated residues and percent crop treated information to estimate the lifetime risk for the general population. The dietary exposure was 0.000005 mg/kg/day and the lifetime dietary risk was  $8.4 \times 10^{-7}$  as there are no uses resulting in post-application.

The aggregate exposure for cancer includes only food and water. Cancer risk estimates associated with exposure to difenoconazole from food and water do not exceed OPP's level of concern.

The estimated average concentrations of difenoconazole in surface and ground

water are less than OPP's DWLOCs for difenoconazole as a contribution to cancer aggregate exposure. Therefore, OPP concludes with reasonable certainty, that residues of difenoconazole in drinking water do not contribute significantly to the aggregate chronic human health risk at the present time considering the present uses and uses proposed in this action. OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate cancer risk assessment process.

## 9. Other Food Quality Protection Act (FQPA) Considerations

### a. Cumulative Risk

**Difenoconazole** is a member of the **triazole** class of pesticides. Other members of this class include cyproconazole, fenbuconazole, propiconazole, tebuconazole, and uniconazole.

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency considers "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments. There are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether difenoconazole has a common mechanism of toxicity with other substances or

how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that difenoconazole has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether difenoconazole share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for difenoconazole need to be modified or revoked.

**b. Endocrine Disruption**

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...". The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

**c. Determination of Safety**

**US Population, Infants, and Children**

Using the exposure assumptions described in this document, HED has concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of difenoconazole is less than 1% of the RfD for all populations. For the acute dietary exposure of the high-risk subpopulation, the % RfD of difenoconazole exposure is not expected to exceed 1% in females (13+ years old). HED has concluded that the excess lifetime cancer risk due to dietary exposure (food only) to residues of difenoconazole is  $8.4 \times 10^{-7}$  for the U.S. population. Despite the potential for exposure to difenoconazole in drinking water, HED does not expect the acute, chronic, or cancer risk to exceed HED's level of concern. HED concludes that there is a reasonable certainty that no harm will result to infants and children from acute, chronic or cancer aggregate exposure to difenoconazole residues.

**III. ACTIONS REQUIRED BY PETITIONER**

**A. Additional Data Requirements**

**1. Toxicological Studies - None**



**2. Chemistry -**

- a. To provide for the re-evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) that additional data be submitted within five years. The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether difenoconazole shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for difenoconazole need to be modified or revoked.

**3. Occupational and Residential Exposure - None**

**IV. REFERENCES**

DP Barcode(s): D205118

Subject: PP# 2F04107. Difenconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 6/30/94.

From: G.F. Kramer, Ph.D., Chemist

To: Cynthia Giles-Parker, PM

Dated: 7/20/94

MRID(s): 432924-01

DP Barcode(s): D203644 and D203645

Subject: PP# 2F04107. Difenconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 5/18/94.

From: G.F. Kramer, Ph.D., Chemist

To: Cynthia Giles-Parker, PM

Dated: 6/16/94

MRID(s): 432365-01 thru -03

DP Barcode(s): D194842, D199810, D199580, and D195868

Subject: PP# 2F04107. Difenconazole (Dividend) in/on Wheat, Barley, and Animal RACs. Review of Residue Data and Analytical Methodology.

From: G.F. Kramer, Ph.D., Chemist

To: Cynthia Giles-Parker, PM and Albin Kocialski, Head

Dated: 3/30/94

MRID(s): 428180-01 thru -06; 422451-41; 422451-01; 431203-01

DP Barcode(s): D172067 and D178394

Subject: PP# 2E4051. CGA-169374 (Difenconazole, Dividend) in Imported Wheat, Barley, and Rye Grain. First Food Use.

From: Robert Lascola, Chemist

To: James Stone/Cynthia Giles-Parker

Dated: 10/26/92

MRID(s): 420900-01 thru -04; 420900-32; 420900-59; 423039-01

DP Barcode(s): D194842, D199810, D199580, and D195868  
Subject: PP# 2F04107. Difenoconazole (Dividend) in/on Wheat and Barley. Results of Petition Method Validation for Animal Commodities.  
From: G.F. Kramer, Ph.D., Chemist  
To: Cynthia Giles-Parker, PM  
Dated: 6/2/94  
MRID(s): 428180-04 thru -05

DP Barcode(s): D210080  
Subject: ID# 000100-00740. Difenoconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 11/21/94.  
From: G.F. Kramer, Ph.D., Chemist  
To: Cynthia Giles-Parker, PM  
Dated: 1/18/95  
MRID(s): 434679-01 thru -03

DP Barcode(s): D217119, D217120, and D217121  
Subject: ID# 000100-00740. Difenoconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 6/29/95.  
From: G.F. Kramer, Ph.D., Chemist  
To: Cynthia Giles-Parker, PM  
Dated: 9/13/95  
MRID(s): 437037-01 thru -02

DP Barcode(s): None  
Subject: PP# 2F04107 and PP#2E4051. Difenoconazole (Dividend). Issues to be presented to the HED Metabolism Committee on 7/14/94  
From: G.F. Kramer, Ph.D., Chemist  
To: HED Metabolism Committee  
Dated: 7/12/94  
MRID(s): None

DP Barcode(s): None  
Subject: Metabolism Committee Meeting of 7/14/94. PP# 2F4107 and PP# 2E4051. Difenoconazole (Dividend).  
From: G.F. Kramer, Ph.D., Chemist  
To: HED Metabolism Committee  
Dated: 7/22/94  
MRID(s): None

DP Barcode(s): D216521  
Subject: PP# 5E04526. Difenoconazole in or on Imported Bananas. Evaluation of Residue Data and Analytical Methods.  
From: G.F. Kramer, Ph.D., Chemist  
To: Cynthia Giles-Parker, PM  
Dated: 2/23/96

MRID(s): 436732-01 thru -14

DP Barcode(s): D229926

Subject: PP# 5E04526. Difenoconazole in or on Imported Bananas. Amendment of 8/20/96. Revised Sections B and F and Submission of Confirmatory Method.

From: G.F. Kramer, Ph.D., Chemist

To: Cynthia Giles-Parker, PM

Dated: 10/4/96

MRID(s): 440933-01 thru -02

DP Barcode(s): D230853

Subject: PP# 5E04526. Difenoconazole in or on Imported Bananas. Amendment of 9/30/96. Revised Section F.

From: G.F. Kramer, Ph.D., Chemist

To: Debbie McCall, Acting Section Head

Dated: 11/13/96

MRID(s): 440933-01 thru -02

DP Barcode(s): D286648

Subject: PP#5E4526. Difenoconazole in or on Imported Bananas. Amendments of 2/21/97 and 3/19/98.

From: Susie Chun, Chemist

To: Cynthia Giles-Parker, PM

Dated: 11/2/98

MRID(s): 445189-00 thru -04.

DP Barcode(s): D248285 and D248419

Subject: PP#2F4107. Difenoconazole (Dividend®) in/on Wheat and Animal RACs. Amendments of 7/8/98 and 7/30/98.

From: Susie Chun, Chemist

To: Cynthia Giles-Parker, PM

Dated: 10/28/98

MRID(s): 446020-00 thru -01; 446194-01.

DP Barcode(s): None

Subject: Difenoconazole - Report of the FQPA Safety Factor Committee.

From: Brenda Tarplee, Executive Secretary

To: Melba Morrow, Branch Senior Scientist

Dated: 10/28/98

MRID(s): None

DP Barcode(s): None

Subject: Difenoconazole - Report of the Hazard Identification Assessment Review Committee.

From: Albin Kocialski, Toxicologist and Jess Rowland, Executive Secretary

To: George Kramer, PhD, Chemist

Dated: 9/25/98  
MRID(s): None

DP Barcode(s): None

Subject: Tier 1 FQPA Drinking Water Assessment for Difenoconazole  
From: James Hetrick, PhD, Senior Physical Scientist  
To: Cynthia Giles-Parker, PM  
Dated: 2/9/99  
MRID(s): None

DP Barcode(s): D251418

Subject: Dietary Exposure Analysis for Difenoconazole in/on Wheat and Animal  
Commodities (2F4107), Import Bananas (5E4526), and Sweet Corn (98ID0040).  
Chemical#: 128847.  
From: Susie Chun, Chemist  
To: Dana Vogel, Chemist  
Dated: 3/11/99  
MRID(s): None

DP Barcode(s): D253277

Subject: PP#5E04526 - Difenoconazole (CGA-169374 Sico 259 EC Fungicide) in/on  
Imported Bananas; and PP#2F4107 - Difenoconazole (Dividend) in/on Wheat and  
Animal RACs. Calculations of Anticipated Residues. PC Code:128847.  
From: Susie Chun, Chemist  
To: Dana Vogel, Chemist  
Dated: 3/11/99  
MRID(s): None

DP Barcode(s): None

Subject: Difenoconazole [Dividend] Quantitative Risk Assessment (Q\*) based on Charles  
River CD-1 mouse chronic dietary study with 3/4's interspecies scaling factor.  
From: Lori Brunsman, Statistician  
To: Albin Kocialski, Toxicologist  
Dated: 12/8/98  
MRID(s): None

DP Barcode(s): None

Subject: Carcinogenicity Peer Review of Difenoconazole [Dividend]  
From: Jess Rowland, Toxicologist and Esther Rinde, Ph.D  
To: Cynthia Giles-Parker, PM  
Dated: 7/27/94  
MRID(s): None

DP Barcode(s): D189836

Subject: Difenoconazole: Registrant's Response to Deficiencies Cited in Toxicology  
Review.

From: Jess Rowland, M.S., Acting Section Head  
To: Cynthia Giles-Parker, PM  
Dated: 9/15/93  
MRID(s): 42710010, 42710008, 42710006, 4271005, 42090014 thru 20

**(No Accompanying Memo Located)**

DP Barcode(s): N/A  
Subject: Difenoconazole: 13-week Feeding Study in Rats  
From: Ciba-Geigy Corporation  
To:  
Dated: 1987  
MRID(s): 429090022

**(No Accompanying Memo Located)**

DP Barcode(s): N/A  
Subject: Difenoconazole: 28-week Feeding Study in Dogs  
From: Ciba-Geigy Corporation  
To:  
Dated: 1987  
MRID(s): 429090012

**(No Accompanying Memo Located)**

DP Barcode(s): N/A  
Subject: Difenoconazole: 13-week Feeding Study in Mice  
From: Ciba-Geigy Corporation  
To:  
Dated: 1987  
MRID(s): 429090021

**(No Accompanying Memo Located)**

DP Barcode(s): N/A  
Subject: Difenoconazole: 13-week Feeding Study in Rats  
From: Ciba-Geigy Corporation  
To:  
Dated: 1987  
MRID(s): 429090022

**(No Accompanying Memo Located)**

DP Barcode(s): N/A  
Subject: Difenoconazole: 21-day Dermal Study in Rabbits  
From: Ciba-Geigy Corporation  
To:  
Dated: 1987  
MRID(s): 429090013

Study: Potential Exposure of Commercial Seed-treating Applicators to the Pesticides

Carboxim-Thiram and Lindane.  
Authors: W.E. Grey, D.E. Marthre, S.J. Rogers  
Location: Bulletin of Environmental Contamination and Toxicology 31, 244-250.  
Dated: 1983

ATTACHMENTS

- I. Dietary exposure analyses for Difenoconazole, 3/11/99

cc: PP#5E04526,PP#2F4107, S. Chun, A. Kocialski, D. Vogel  
RDI: Team (11/18/98, 3/16/99), RAB1 Chemists (11/19/98, 3/11/99); M. Morrow (11/17/98); Risk SARC (12/1/98)  
D. Vogel: 804F:CM#2:(703)305-0874