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

OFFICE OF PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

February 9, 2006

MEMORANDUM

SUBJECT: **Triadimenol**: HED Chapter of the Tolerance Reassessment Eligibility Decision (TRED) Document (Revised)
PC Code: 127201, CAS Reg. No. 55219-65-3, DP Barcode: D326716

Regulatory Action: Tolerance Reassessment Eligibility Decision
Risk Assessment Type: Single Chemical/Aggregate

FROM: Christina Jarvis, Risk Assessor
Richard Griffin, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

AND

Judy Facey, Toxicologist
Yvonne Barnes, Product Chemist
Samuel Ary, Residue Chemist
Reregistration Branch II
Health Effects Division (7509C)

THROUGH: Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)

TO: John Pates, Jr., Chemical Review Manager
Reregistration Branch III
Special Review and Reregistration Division (7508C)

TABLE OF CONTENTS

1.0 SUMMARY

This chapter represents the Health Effects Division's (HED's) chapter of the Tolerance Reassessment Eligibility Decision (TRED) document for triadimenol. A TRED is prepared for pesticides registered after 1984, and reports on FQPA tolerance reassessment progress. As such, a TRED does not include an assessment of occupational uses of, and occupational risk to, a particular pesticide.

Triadimenol [β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol] is a systemic fungicide registered for use in the United States as a seed treatment for barley, corn, cotton, oats, rye, sorghum, and wheat. Additionally, an import tolerance on bananas has been established. Triadimenol end-use products are marketed in the U. S. under the trade name Baytan®. The reregistration of triadimenol is being supported by Bayer CropScience, the basic producer. The triadimenol formulations registered for food/feed uses include emulsifiable concentrate (EC), wettable powder (WP), flowable concentrate (FlC), and soluble concentrate (SC) formulations.

Tolerances are established for residues of triadimenol and its butanediol metabolite (KWG 1342, calculated as triadimenol) in/on various plant commodities. The established tolerances for plant commodities range from 0.01 ppm (sorghum grain and fodder) to 2.5 ppm (green forage of oats, rye, and wheat). Tolerances are currently established for residues of triadimenol and its metabolites containing the chlorophenoxy moiety (calculated as triadimenol) in/on livestock commodities at 0.01 ppm (milk, and poultry commodities) and 0.1 ppm (fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep). However, the Agency has determined that a 40CFR 180.6(a)(3) situation exists for the livestock commodities and those tolerances will be revoked. Triadimenol and its butanediol metabolite are also regulated as metabolites of the fungicide triadimefon.

The toxicological database for triadimenol contains acceptable / guideline toxicity studies including acute, subchronic (rats and dogs), developmental (rats and rabbits), chronic (dog), two carcinogenicity (mice) studies, a chronic/carcinogenicity study in rats, a 15-day dermal study in rats, a two year reproduction study in rats, and a central nervous effects study in mice and rats. The database is also supported by substantial data from the literature, including some studies performed by EPA scientists, that support the mode of toxic action and endpoint selection.

Triadimenol shows low toxicity for acute oral, dermal, and inhalation exposures (toxicity Category III or IV) and is not a skin sensitizer. Triadimenol is an eye irritant with irritation clearing in 21 days or longer (toxicity Category II), and is a mild dermal irritant (toxicity Category IV). For the purposes of reregistration, the database is adequate although there are data gaps (lack of acute and subchronic neurotoxicity studies).

There was no evidence for quantitative and qualitative susceptibility following oral or dermal exposures to rats *in utero* or oral exposure to rabbits *in utero*. The degree of concern for pre-

and/or post-natal susceptibility is low.

HED's Cancer Assessment Review Committee (CARC) has classified triadimenol as a category C, "possible human carcinogen." This classification is based on increased incidence of hepatocellular adenomas in females. However, it was concluded that a quantified carcinogenic risk assessment for triadimenol is not appropriate and risk assessment will be based on the chronic population adjusted dose (cPAD) and margin of exposure (MOE) approaches only.

The special Food Quality Protection Act (FQPA) safety factor of 10x is not required since the current developmental and reproductive toxicity studies do not suggest that the young are more sensitive than adult animals, and the lack of a developmental neurotoxicity study is addressed by the FQPA database uncertainty factor of 10x. The FQPA Safety Factor is 1x.

No appropriate acute and chronic endpoint could be determined from the triadimenol database; therefore, the *triadimefon* subchronic neurotoxicity study in rats was chosen as the basis for the acute and chronic Reference Doses (aRfD/cRfD). The Lowest-Observed-Adverse-Effect-Level (LOAEL) of 54.6♂ and 68.7♀ mg/kg/day is based on hyperactivity. The No-Observed-Adverse-Effect-Level (NOAEL) is 3.4♂ and 4.3♀ mg/kg/day. For acute and chronic dietary risk assessments, the uncertainty factor is 1,000X (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X FQPA database uncertainty factor). Since the *special* FQPA safety factor is reduced to 1X, the aRfD/cRfD of 0.0034 mg/kg/day is equivalent to the acute/chronic population adjusted dose (aPAD/cPAD).

The Agency has determined that the residues of concern for tolerance expression and risk assessment are likely to be triadimenol, the metabolite KWG 1342, and the metabolite KWG 1732 in/on cereal grains (barley, corn, oats, rye, and wheat) and cotton. The residues of concern for tolerance expression and risk assessment for bananas are triadimenol and the metabolite KWG 1342. Based on an analysis of the structural relationship of the above metabolites to parent triadimefon, the toxicity of metabolites is not expected to exceed the parent compound, and an assumption of equal toxicity is made for aggregate risk assessment.

Acute and chronic dietary (food and water) exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The acute dietary risk assessment utilizes anticipated residue estimates for bananas, tolerance level residues for all other commodities, a default processing factor for dried bananas, available data from processing studies, and a 100% crop treated assumption, as well as peak surface water concentration values. For all supported commodities, the acute dietary (food + water) risk estimates do not exceed HED's level of concern (less than 100% of the aPAD) at the 95th exposure percentile for the U.S. population and all populations subgroups. The highest exposed population subgroup is children 1-2 years of age at 29% of the aPAD.

A chronic dietary exposure assessment was conducted, using existing tolerance level residues, a default processing factor for dried bananas, available data from processing studies, an assumption of 100% crop treated, and the highest 1 in 10 year annual mean drinking water concentration. For all supported commodities, the chronic dietary risk estimates (food + water) do not exceed HED's level of concern for the U.S. population and all population subgroups. The highest exposed population subgroup is children 1-2 years of age at 23% of the cPAD.

A Tier II drinking water assessment was conducted by OPP's Environmental Fate and Effects Division (EFED), based on parent triadimenol. Parent triadimenol was the major residue found in the available triadimefon aerobic soil metabolism study. Estimated environmental concentrations (EECs) of triadimenol in surface water were generated by the PRZM-EXAMS model and were based on the maximum calculated application rate of triadimenol as a seed treatment for each crop. For drinking water derived from surface water, acute and chronic concentrations are as follows:

- 393 ng/L (acute) and 194 ng/L (chronic) for wheat, barley, oats, and rye
- 95 ng/L (acute) and 34 (chronic) for corn
- 133 ng/L (acute) and 27 ng/L (chronic) for cotton

EFED conducted a Tier 1 assessment of estimated ground water concentrations of triadimenol, using the SCI-GROW2 model. For drinking water derived from ground water, the EECs are 63 ng/L (wheat, barley, oats, and rye), 18 ng/L (corn), and 10 ng/L (cotton). No water monitoring data are available for this compound for comparison to modeled values.

There are no residential uses of triadimenol; therefore, a non-occupational (residential) assessment has not been conducted. The aggregate risk assessment includes combined exposure from food and drinking water only. Aggregate risks from combined exposure to food and drinking water are below HED's level of concern (<100% of the aPAD/cPAD).

2.0 INGREDIENT PROFILE

2.1 Registered Uses / Products

Triadimenol [β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol] is a systemic fungicide registered for use in the United States as a seed treatment for barley, corn, cotton, oats, rye, sorghum, and wheat. Triadimenol end-use products are marketed in the U. S. under the trade name Baytan®. The reregistration of triadimenol is being supported by Bayer Corporation, the basic producer, and by Gustafson, Inc. The triadimenol formulations registered for food/feed uses include emulsifiable concentrate (EC), soluble concentrate (SC), wettable powder (WP), and flowable concentrate (FlC) formulations.

Table 1: Triadimenol End-use Products (EPs) Registered.

EPA Reg. No.	Formulation[1]	Registrant	Product Name
264-742	25% WP	Bayer CropScience	Baytan® Seed Treatment Fungicide
264-760	28.3% FlC	Bayer CropScience	Baytan® 2.6 FS Seed Treatment Fungicide
264-939	5% EC	Bayer CropScience	Gustafson RTU®- Baytan®-Thiram Fungicide
264-941	30% FlC	Bayer CropScience	Gustafson Baytan® 30 Fungicide
264-980	13.33 SC	Bayer CropScience	Protege Allegiance Bayton® W.P. Fungicide
2935-459	30% FlC	Wilbur-Ellis Company	Wilbur-Ellis Baytan® Flowable

1. WP=Wettable Powder, FlC=Flowable Concentrate, EC=Emulsifiable Concentrate, and SC=Soluble Concentrate.

2.2 Use Patterns / Rates

Triadimenol is used as a seed treatment on wheat, barley, oats, rye, corn, and cotton. The maximum use rates, adjusted for planting rate, range from 0.006 to 0.0375 lb ai/A (0.007-0.042 kg ai/ha) for one season (see Table 2 below).

Table 2: Maximum Application / Seeding Rates				
End-uses (planting depth)	**Max. Label Rates (lb ai/100 lb seed)**	**# Apps**	**Seeding Rates (lbs/A)[1]**	**Seasonal Max. Rate (kg ai/Ha, including planting rates)**
Baytan 2.6 FS				
Wheat	0.03 (all crops)	1	70-125	0.024-0.042
Barley		1	60-80 (Plains) 80-100 (CA) 50-60 (drier areas)	0.02-0.027 0.027-0.034 0.017-0.02
Oats		1	60-100	0.02-0.034
Gustafson (RTU-Baytan-Thiram), 0.43 lb triadimenol/gallon				
Wheat	0.015-0.03 (all crops)	1	70-125	0.024-0.042
Barley		1	60-80 (Plains) 80-100 (CA) 50-60 (drier areas)	0.02-0.027 0.027-0.034 0.017-0.02
Oats		1	60-100	0 02-0.034
Rye		1	41 (CO)-86 (GA)	0.013-0.029
Cotton (acid delinted)	0.01-0.04	1	10[2]	0.002-0.007
Baytan 30 (2.65 lb ai/gallon)				
Wheat	0.015-0.03	1	70-125	0.024-0.042
Barley		1	60-80 (Plains) 80-100 (CA) 50-60 (drier areas)	0.02-0.027 0.027-0.034 0.017-0.02
Oats		1	60-100	0.02-0.034
Rye		1	41 (CO)-86 (GA)	0.013-0.029
Corn	0.06	1	19[3]	0.012
Cotton	0.021-0.06	1	10[2]	0.002-0.007

[1] Unless otherwise noted, the information comes from Considine, D.M. and G.D. Considine. Foods and Food Production Handbook. 1982. Van Nostrand Reinhold Company.
[2] Based on http://www.agctr.lsu.edu/cotton/SEEDRATE.html
[3] Iowa Extension Service

2.3 Percent Treatment of Registered Crops

Based on pesticide usage data for the years 1992 through 2001, total annual domestic usage of triadimenol averaged approximately 24,000 pounds of active ingredient (a.i.) for over 12,000,000 acres treated. Use on cotton accounted for approximately 75 % of the total pounds of a.i. applied annually. Corn and wheat accounted for approximately 20% and 5%, respectively. About 80% of U.S. acreage planted to cotton is treated with triadimenol, and less than 1 % of corn and wheat acres are treated (F. Hernandez memo, 8/5/02).

2.4 Structure / Physicochemical Properties

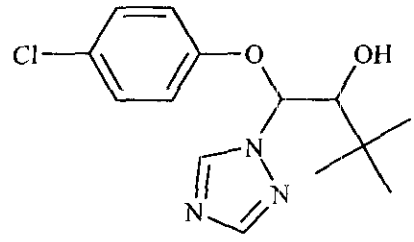
Table 3: Triadimenol Nomenclature.	
Chemical structure	
Common name	Triadimenol
Molecular formula	$C_{14}H_{18}ClN_3O_2$
Molecular weight	295.77 g/mol
IUPAC name	(1RS,2RS;1RS,2SR)-1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol
CAS name	β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol
CAS number	55219-65-3
PC Code	127201
Current supported food/feed sites	barley, cotton, corn, oats, rye, and wheat

Table 4: Physicochemical Properties of Triadimenol		
Parameter	Value	Reference
Melting point/range	109-115°C	MRID 00125399
pH	Not available	--
Density at 20°C	1.22 g/mL	MRID 00125399
Water solubility at 20°C	0.012 g/100g of water	MRID 00125399
Solvent solubility at 20°C	Triadimenol is insoluble in aliphatic hydrocarbons. 1 to 5 g/100g of toluene 10 to 20 g/100g of methylene chloride 40 to 60 g/100g of cyclohexanone	MRID 00125399
Vapor pressure at 20°C	<1 mPa	MRID 00125399
Dissociation constant, pK_a	Not available	--

Table 4: Physicochemical Properties of Triadimenol		
Parameter	Value	Reference
Octanol/water partition coefficient	Not available	--
UV/visible absorption spectrum	Not available	--

Triadimenol contains two optically active carbons, and consists of four optically active isomers. The registrant has stated that the product consists of two pairs of enantiomers, one pair of which is five times more active than the other. The product is manufactured to maximize the fraction of the more pesticidally active enantiomer pair.

2.5 Data Requirements

The following product chemistry data requirements are identified for triadimenol:

- OPPTS Guideline 830.6313, Normal and elevated temperatures, and upon exposure to metals and metal ions
- OPPTS Guideline 830.7000, pH
- OPPTS Guideline 830.7050, UV/VIS Absorption
- OPPTS Guidelines 830.7550, 830.7560, or 830.7570, N-octanol/water partition data
- OPPTS Guideline 830.7840 or 830.7860, water solubility

3.0 METABOLISM ASSESSMENT

Two triadimenol specific metabolism studies (wheat and sugar beets) have recently been submitted and are currently under review by the Agency. Metabolism studies with *triadimefon* have been received and reviewed, and are used to determine residues of concern in/on apples, grapes, pears, pineapples, and raspberries. The Agency believes that the use of triadimefon metabolism data for triadimenol is appropriate in this case, given that triadimenol is a major metabolite of triadimefon, and given that the two compounds are structurally similar.

The exception to this is for cereal grains and cotton. HED has determined that the translation of metabolism data from triadimefon to triadimenol is not appropriate for existing uses on cereal grains and cotton, since metabolism studies with triadimefon were conducted using a foliar application and triadimenol is used only as a seed treatment.

The triadimefon/triadimenol metabolite, 1,2,4-triazole, occurs in other triazole pesticides and a risk assessment specific to 1,2,4,-triazole is currently being conducted by the Agency. It should also be noted that, except for 1,2,4-triazole, specific toxicological data are not available for the other triadimefon/triadimenol metabolites (KWG 1323, KWG 1342, and KWG 1732) identified in metabolism studies. However, based on an analysis of the structural relationship of the above metabolites to triadimefon/triadimenol, the toxicity of metabolites is not expected to exceed the

parent compound, and an assumption of *equal* toxicity is made for aggregate risk assessment.

3.1 Metabolism in the Rat

In a rat metabolism study, [^{14}C] triadimefon (radiochemical purity not reported) in 50% aqueous ethanol was administered as a single gavage dose at 24.5-25.0 mg/kg to 12 Sprague Dawley rats/sex to determine tissue distribution and to 12 rats/sex to determine the excretion profile. Radioactivity was not detected in the expired air of animals. Over a 7 day-period, recovery in the urine was 29.8% dose in males and 39.9% in females, and recovery in feces was 52.7% in males and 34.5% in females. Thus, based on urinary excretion, absorption was at least 29.8% dose in all animals. Plasma levels of radioactivity were highest 1-2 hours post-dose (2.5-3.2 ppm), and the half-life was approximately 4 hours. Tissue concentrations in males were generally similar to females. The highest concentrations of radioactivity were found in the fat (43.5-45.0 ppm) at 4-8 hours post-dose. Approximately 50% of the radiolabeled compound in the fat of males was unchanged triadimefon and 50% was isomeric forms of the 2-butanol derivative (triadimenol); over 90% was triadimefon in females. In addition, relatively high concentrations of radioactivity were observed in the liver (26.2-28.4 ppm) and skin (21-22 ppm) at 2 hours post-dose. Tissue concentrations were <0.14 ppm at 7 days post-dose. In the urine, the major component of the acidified extract was KWG 0519 acid (6.1-7.7% dose). In the direct extract of urine, 3 minor metabolites were identified: p-chlorophenol, KWG 1323, and KWG 1342 (two isomers). In the direct extract of the feces, KWG 1323, KWG 1342, and KWG 0519 acid (5.7-20.0% dose) were identified. KWG 1323 was the predominant metabolite in the feces of females (12.7% dose), and KWG 0519 acid was the predominant metabolite in the feces of males (20.0% dose). Thus, the major metabolites were the alcohol and acid of triadimefon, which were formed by the sequential hydroxylation and oxidation of the methyl group of the t-butyl chain.

In a second rat metabolism study, [^{14}C] triadimefon (99.3% radiochemical purity) in polyethylene glycol was administered to 5 Wistar rats/sex/dose as a single gavage dose at 5 or 50 mg/kg or as a single gavage dose at 5 mg/kg following 14 daily doses of unlabeled triadimefon at 5 mg/kg. In addition, triadimefon was administered to a group 3 of male rats as a single gavage dose of 50 mg/kg in a preliminary study. Radioactivity was not detected in the expired air. The overall recovery of radioactivity was 97-112%. The compound was predominantly excreted (90-98% dose) within 4 days. The excretion profile of the repeated low-dose group was similar to the single low-dose group; however, the excretion profiles were sex-dependent. Over a 4-day period, recovery in the urine was 24-28% dose in males and 57-66% in females, and recovery in feces was 63-66% in males and 32-40% in females. Thus, based on urinary excretion, absorption was at least 24% dose in males and 57% in females. Less than 1% dose remained in the body 4 days after treatment. Bioaccumulation was not indicated. Tissue residues were highest in the liver (0.088-1.94 ppm) and kidney (0.041-0.38 ppm), and were generally slightly higher in males than in females. RP-HPLC analyses revealed the presence of 15 radioactive components in the urine and 12 in the feces. The 4 major metabolites (1-14% dose, each) in the urine of both sexes were: KWG 0519 acid (2 isomers), KWG 1323-gluc, HO-DeME-KWG 1342 (2 isomers), and DeMe- KWG 132-gluc (2 isomers). The 5 major metabolites (1-15% dose, each) in the feces of

both sexes were: KWG 0519 acid (2 isomers), KWG 1323-gluc, KWG 1323, KWG 1342, and KWG 0519 dehydrate. Thus, metabolism of this compound proceeded along several pathways, such as: (i) hydroxylation at the t-butyl moiety and oxidation to the acid or glucuronidation; (ii) reduction of the keto group and subsequent reactions (including sulfate conjugation); and (iii) desmethylation followed by glucuronidation.

3.2 Metabolism in Plants

The reregistration requirements for plant metabolism have not been fulfilled. Two metabolism studies with triadimenol (wheat and sugar beets) have been submitted and are currently under review by the Agency. Additionally, metabolism studies with triadimefon (grapes, cucumbers, tomatoes, and wheat) have been received and reviewed. The Health Effects Division (HED) has examined the results of these studies and determined that the triadimefon residues of concern in/on apples, grapes, pears, pineapples, and raspberries for tolerance expression are triadimefon and triadimenol. The residues of concern for risk assessment are triadimefon, triadimenol, KWG 1323, and KWG 1342. Of these compounds, triadimenol and KWG 1342 are currently regulated for plant commodities.

HED has determined that the translation of metabolism data from triadimefon to triadimenol is not appropriate for existing uses on cereal grains and cotton. The metabolism studies with triadimefon were conducted using a foliar application, while triadimenol is used only as a seed treatment. Additionally, in the submitted triadimenol seed treatment wheat study, residues in grain were not identifiable due to the low activity found in wheat grain. Therefore, HED concludes the nature of the residue in cereal grains and cotton is not adequately understood; however, based on chemical structure and the probable metabolic pathway of triadimenol, the residues of concern for tolerance expression and risk assessment are likely to be triadimenol, KWG 1342, and KWG 1732 in/on cereal grains (barley, corn, oats, rye, and wheat) and cotton. Separate metabolism studies with triazole-^{14}C and phenyl-^{14}C labeled triadimenol applied as a seed treatment to corn or wheat and cotton should be conducted to confirm the residues of concern.

The residues of concern for tolerance expression and risk assessment for bananas are triadimenol and KWG 1342, based on the available metabolism data conducted with triadimefon, applied to an established grape vine, and the field trial data conducted with triadimenol applied to the soil of banana groves.

3.3 Metabolism in Livestock

The metabolism of triadimefon/triadimenol in livestock is adequately understood based on acceptable goat and poultry metabolism studies submitted to support reregistration of triadimefon.

For the ruminant study, a lactating goat received [phenyl-^{14}C]triadimefon at 86.4 ppm for three

consecutive days in feed. Triadimefon was detected at low levels in milk and fat (<5% TRR) but was not detected in kidney, liver, or muscle. The major residue identified was KWG 1342 glucuronide (6-47% TRR). Triadimenol and its conjugates comprised a major portion of the residue in tissues and milk (totals of 9-42% TRR). The remainder of the radioactivity was identified as KWG 1323 glucuronide (19-22% TRR) and KWG 1342 (1-6% TRR) and its sulfate (1-15% TRR in tissues, 43% TRR in milk).

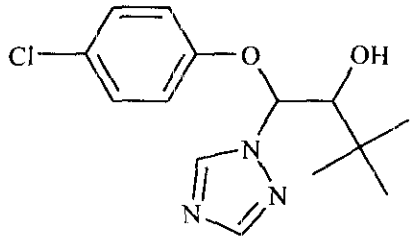
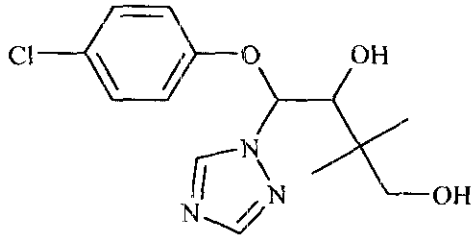
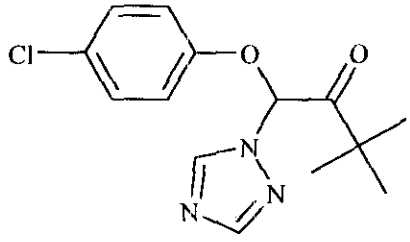
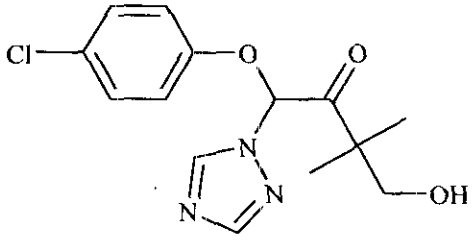
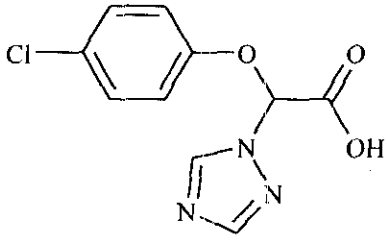
For the poultry study, 16 laying hens received [phenyl-^{14}C]triadimefon at 28.7 ppm for three consecutive days in feed. Triadimefon was identified in fat and eggs (4-17% TRR) but was not detected in liver or muscle. Triadimenol and its related compounds were the major metabolites identified (totals of 41-49% TRR). The remainder of the radioactivity was identified as KWG 1342 and its related compounds (totals of 10-36% TRR), p-chlorophenol (liver and fat only at 2-4% TRR), chlorophenoxytriazolyl acetic acid (muscle only at 3% TRR), and KWG 1323 (eggs and fat only at 3-5% TRR).

HED concludes that the supported uses on barley, corn, cotton, oats, rye, and wheat result in a 40 CFR 180.6(a)(3) situation for livestock commodities; i.e, there is no reasonable expectation of finite residues in livestock commodities. Additional data on the transfer of residues to meat, milk, poultry, and eggs are not required and all tolerances for livestock commodities should be revoked pending results from the requested corn and wheat metabolism studies. If registration on additional commodities and livestock feed items are requested, then triazole and phenyl-labeled livestock metabolism studies would be required. Such data may, in turn, trigger the need for magnitude of the residue (feeding) studies in livestock.

3.4 Metabolism / Degradation in the Environment

Based on laboratory studies and the submitted field dissipation study, triadimenol is stable in sterile water and to photodegradation on soil, but may photodegrade in shallow, well-mixed surface water that is not shaded or contains a significant sediment load. The primary route of triadimenol degradation appears to be microbial activity. Triadimenol degraded slowly in aerobic soil in the laboratory, with a calculated half-life of 238 days. Triadimenol does not degrade under anaerobic conditions and appears to be mobile in soil (Kd=2.4-5.3). Since triadimenol is a seed treatment only, and applied below the soil surface, runoff to surface water may be reduced but the potential for groundwater contamination may be increased.

Table 5: Chemical Names and Structures of Triadimenol and Its Metabolites.

Common name and chemical name	Chemical structure
Triadimenol (KWG 0519) β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol	
KWG 1342 1-(4-chlorophenoxy)-3,3-dimethyl-3-hydroxymethyl-1-(1H-1,2,4-triazole-1-yl)-2-butanol	
Triadimefon 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazole-1-yl)-2-butanone	
KWG 1323 1-(4-chlorophenoxy)-3,3-dimethyl-3-hydroxymethyl-1-(1H-1,2,4-triazole-1-yl)-2-butanone	
KWG 1732 1-(4-chlorophenoxy)-1-(1H-1,2,4-triazole-1-yl)ethanoic acid	

3.5 Summary of Residues for Tolerance Expression and Risk Assessment

3.5.1 Tabular Summary

Table 6: Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary crop - cereal grains and cotton	triadimenol, KWG 1342, and KWG 1732	triadimenol, KWG 1342 and KWG 1732
	Primary crop - bananas	triadimenol and KWG 1342	triadimenol and KWG 1342
	Rotational crop	triadimenol, KWG 1342, and KWG 1732	triadimenol, KWG 1342, and KWG 1732
Livestock	Ruminant	NA	NA
	Poultry	NA	NA
Drinking Water		triadimenol	NA

NA = Not Applicable

4.0 HAZARD CHARACTERIZATION / ASSESSMENT

4.1 Hazard Profile

Table 7: Acute Toxicity Profile - Triadimenol Technical

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral -rat	00125411	LD_{50} = 689 mg/kg (males) LD_{50} = 752 mg/kg (females)	III
870.1200	Acute dermal - rabbit	00145086	LD_{50} > 2000 mg/kg	III
870.1300	Acute inhalation - rat	00145087	LC_{50} > 2.58 mg/L (Limit Dose)	IV
870.2400	Acute eye irritation - rabbit	00145088	eye irritant. Irritation cleared in 21 days or longer.	II
870.2500	Acute dermal irritation - rabbit	00145088	mild skin dermal irritation	IV

870.2600	Skin sensitization- guinea pig	00125413	Not a skin sensitizer	Not Applicable

Table 8: Triadimenol Technical Toxicology Profile

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents (rats)	00127769 (1977) Acceptable/guideline 0, 150, 600, or 2400 ppm M: 0, 12.16, 49.23, 203.07 mg/kg/day F: 0, 17.07, 71.33, 236.60 mg/kg/day	NOAEL is 600 ppm (equivalent to 49.23/71.33 mg/kg/day [M/F]). The LOAEL is 2400 ppm (equivalent to 203.07/236.60 mg/kg/day [M/F]) based on initial body weight decreases in both sexes.
	42192701 (1983) Acceptable/guideline 0, 120, 600, or 3000 ppm M: 0, 8.0, 39.6, 208.5 mg/kg/day F: 0, 9.4, 46.4, 221.1 mg/kg/day	NOAEL is 120 ppm (equivalent to 8.0/9.4 mg/kg/day in the males/females). The LOAEL for this study is 600 ppm (equivalent to 39.6/46.4 mg/kg/day in the males/females) based on increased liver weights and incidences of liver hypertrophy in the males and females and on fatty changes in the liver in the females.
870.3150 90-Day oral toxicity (non-rodents- dogs)	00125420 (1977) Acceptable/guideline 0, 150, 600, or 2400 ppm M: 0, 44.2, 178.5, or 717.0 mg/kg/day F: 0, 44.8, 179.0 or 702.1 mg/kg/day	NOAEL is 600 ppm (equivalent to 44.2/44.8 mg/kg/day in the males/females). The LOAEL for this study is 2400 ppm (equivalent to 717.0/702.1 mg/kg/day in the males/females) based on decreased body weights and body weight gains in the females, increased alkaline phosphatase, cholesterol, absolute kidney weights, and renal cysts in the males, and increased N-demethylase and relative liver weights in the males and females.
870.3150 6 months oral toxicity (non- rodents- dogs)	00151247 (1984) Acceptable/guideline 0, 10, 30, or 100 ppm 0, 0.25, 0.75, or 2.5 mg/kg/day	NOAEL is 100 ppm (approximately equivalent to 2.5 mg/kg/day). The LOAEL was not observed.

Table 8: Triadimenol Technical Toxicology Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200 15-Day dermal toxicity (rabbits)	00151246 (1984) Acceptable/guideline 0, 50, or 250 mg/kg/day	NOAEL is 250 mg/kg/day for males and females. The LOAEL was not observed.
870.3465 21-Day inhalation toxicity (rats)	00125421 (1976) Unacceptable/not ungradable 0, 30, 68, or 230 mg/m^3 0, 0.030, 0.068, or 0.230 mg/L	NOAEL is 0.230 mg/L/day, the highest dose tested. The LOAEL was not observed.
870.3700a Prenatal developmental in (rats)	41498401 (1990) Acceptable/guideline 0, 5, 15, 25, or 60 mg/kg/day	Maternal NOAEL is 5 mg/kg/day and the LOAEL is 15 mg/kg/day based on decreased body weights and adjusted (for gravid uterine weight) body weight gains. Developmental NOAEL is 25 mg/kg/day and the LOAEL is 60 mg/kg/day based on increased incidences of extra ribs, a variation.
	40307804 & 40887702 (1987) Acceptable/guideline 0, 30, 60, or 120 mg/kg/day	Maternal NOAEL is 30 mg/kg/day and the LOAEL is 60 mg/kg/day based on decreased body weights, body weight gains, and food consumption. Developmental NOAEL is 30 mg/kg/day and the LOAEL is 60 mg/kg/day based on increased incidences of supernumerary ribs.

Table 8: Triadimenol Technical Toxicology Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b Prenatal developmental in (rabbits)	42365001 (1992) Acceptable/guideline 0, 5, 25, or 125 mg/kg/day	Maternal NOAEL is 25 mg/kg/day and the LOAEL is 125 mg/kg/day based on decreased body weights, body weight gains, and food consumption. Developmental NOAEL is 125 mg/kg/day (HDT). The developmental LOAEL was not observed.
	40307805 & 40887703 (1987) Acceptable/guideline 0, 8, 40, or 200 mg/kg/day	Maternal NOAEL is 40 mg/kg/day and the LOAEL is 200 mg/kg/day based on clinical signs of toxicity, decreased body weights and food consumption, and increased post-implantation loss and early resorptions. Developmental NOAEL is 40 mg/kg/day and the LOAEL is 200 mg/kg based on skeletal abnormalities.
870.3800 Reproduction and fertility effects (rats)	00151248 (1984) Acceptable/ guideline 0, 20, 100, or 500 ppm (0, 1, 5 or 25 mg/kg/day)	Parental/Systemic toxicity NOAEL is 5 mg/kg/day and the LOAEL is 25 mg/kg/day based on decreased body weights and body weight gains in the F1b generation. Offspring toxicity NOAEL is 5 mg/kg/day and the LOAEL is 5 mg/kg/day based on decreased pup weight. Reproductive toxicity NOAEL appears to be 5 mg/kg/day The LOAEL for reproductive performance was not observed.
870.4100b Chronic toxicity (dog)	00150484 & 00159012 (1984) Acceptable/non-guideline 0, 150, 600, or 2400 ppm 0, 3.8, 15.0, or 60.0 mg/kg/day	The NOAEL is 3.8 mg/kg/day and the LOAEL is 15 mg/kg/day based on changes in enzyme levels.

Table 8: Triadimenol Technical Toxicology Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200 Carcinogenicity (mice)	44740901 (1998) Unacceptable/guideline 0, 80, 400, or 2000 ppm M: 0, 11.3, 60.2, or 340.3 mg/kg/day F: 0, 17.2, 91.3 or 472 mg/kg/day	NOAEL in males is 80 ppm (equivalent to 11.3 mg/kg/day) and in females is 400 ppm (equivalent to 91.3). LOAEL in males is 400 ppm (equivalent to 60.2 mg/kg/day) based on hepatic changes and increased relative food consumption. The chronic LOAEL in females is 2000 ppm (equivalent to 472.0 mg/kg/day) based on decreased body weights and body weight gains, increased relative food consumption, and hepatic changes. No evidence of carcinogenicity
870.4200 Carcinogenicity (mice)	00126259 (1982) Acceptable/guideline 0, 125, 500, or 2000 ppm 0, 19, 75, or 300 mg/kg/day	The NOAEL is 125 ppm (equivalent to 19 mg/kg/day). The LOAEL is 500 ppm (equivalent to 75 mg/kg/day), based on increased alanine aminotransferase levels in both sexes and aspartate aminotransferase in females. At the doses tested, the carcinogenic potential of KWG 0519 is positive at 500 ppm. Hepatic neoplastic lesions occurred in females due to treatment. The incidence of adenomas increased dose-dependently (2-10% treated vs 0% concurrent controls and 4% historical controls). The incidence of hepatic carcinoma was increased at 500 and 2000 ppm (4-6% treated vs 2% concurrent controls). The incidence of combined hepatic adenomas and carcinomas was also increased at 500 and 2000 ppm (10-16% treated vs 2% controls). The Toxicology Branch Peer Review Committee (TXR #006772, dated July 6, 1988) concluded that KWG 0519 should be classified as a Group C carcinogen. Dosing was considered adequate based on decreased body weights, and increased blood levels of hepatic enzymes and liver weights, and increased incidences of gross and microscopic abnormalities.

Table 8: Triadimenol Technical Toxicology Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300 Combined Chronic/Carcinogenicity (rats)	00126260 (1982) Acceptable/guideline 0, 125, 500, or 2000 ppm 0, 6.25, 25, or 100 mg/kg/day	The NOAEL is 125 ppm (approximately equivalent to 6.25 mg/kg/day). The LOAEL is 500 ppm (approximately equivalent to 25 mg/kg/day), based on increased glutamate dehydrogenase and liver bile duct vacuolization in males; and aspartate and alanine aminotransferase levels in females. no evidence of carcinogenicity
870.5100 Bacterial system, mammalian activation gene mutation	00126264 (1979) Unacceptable/ guideline 0, 4, 20, 100, 500, or 2500 µg/plate (+S9) and 2500 µg/plate (-S9)	Negative
870.5300 *In Vitro* Mammalian Cell Gene Mutation	00126269 (1982) Acceptable/ guideline 7.8, 15.6, 31.3, 62.5, or 125.0 µg/mL (-S9) 3.91, 7.81, 15.6, 31.3, or 62.5 µg/mL (+S9)	Negative
870.5450 Cytogenetics dominant lethal assay	00126266 (1978) Unacceptable/up- gradable 0 or 500 mg/kg	Negative
870.5500 Other Genotoxicity DNA damage	00126271 (1981) Acceptable/guideline 0, 62.5, 125, 250, 500, or 1000 µg/plate	Negative no evidence that DNA damage was induced
870.5550 Other Genotoxicity Unscheduled DNA Synthesis	00126271 (1982) Acceptable/guideline 0, 0.25, 0.5, 1, 2.5, 5, 10, 25, 50, 100, or 250 µg/mL.	Negative no evidence that unscheduled DNA synthesis
870. 5900 Other Effects *In vitro* Sister Chromatid Exchange Assay	40815901 (1987) Acceptable/guideline 0, 100, 125, 150, 175, or 200 µg/mL (+S9) 0, 38, 75, 150, 225, or 300 µg/mL (-S9)	Negative

Table 8: Triadimenol Technical Toxicology Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Other Studies Central Nervous Effects (mouse)	00145083 (1983) 3.75 to 60 mg/kg	In mice, KWG 0519 (3.75 to 60 mg/kg) stimulated the spontaneous motility, increased their irritability and escape response and augmented certain reflexes; dose of 15 and 60 mg/kg potentiated the effect of amphetamine; and doses of 12 to 48 mg/kg antagonized that of reserpin. The substance prolonged the hexobartital sleeping time at 15 and 60 mg/kg. In rats, the dose of 48 mg/kg had an excitatory effect. An comparison with caffeine showed that the effect fo the dose of 2.5 mg caffeine/ kg corresponded approximately to that of 12 to 15 mg/ KWG 0519/ kg, in the amphetamine potentiation test that of 4 mg KWG 0519/ kg, in the antagonism of ptosis 10 mg caffeine/ kg and 12 mg KWG 0519/ kg were comparable. The no- effect dose was ca. 1 mg/kg.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

4.2.1.1 Studies available and considered (animal, human, and general literature)

The toxicological database for triadimenol contains acceptable / guideline toxicity studies including acute, subchronic (rats and dogs), developmental (rats and rabbits), chronic (dog), two carcinogenicity (mice) studies, a chronic/carcinogenicity study in rats, a 15-day dermal study in rats, a two year reproduction study in rats, and a central nervous effects study in mice and rats. The database is also supported by substantial data from the literature, including some studies performed by EPA scientists, that support the mode of toxic action and endpoint selection.

Triadimenol shows low toxicity for acute oral, dermal, and inhalation exposures (toxicity Category III or IV) and is not a skin sensitizer. Triadimenol is an eye irritant with irritation clearing in 21 days or longer (toxicity Category II), and is a mild dermal irritant (toxicity Category IV). For the purposes of reregistration, the database is adequate although there are data gaps (lack of acute and subchronic neurotoxicity studies).

The endpoint of concern is neurotoxicity. Although there is a central nervous effect study conducted with triadimenol, the study is not a comprehensive study. Based on the available data on the similar effects, similar structure, and similar mode of action of triadimefon and

triadimenol, the current triadimefon neurotoxicity studies (acute (ACN) and subchronic neurotoxicity (SCN) studies) will be used to establish the triadimenol acute and chronic reference doses. Please see section 4.2.1.2 through 4.2.3 below for more detail.

4.2.1.2. Evidence of Neurotoxicity (Mode of action, metabolism, toxicokinetic data)

The active ingredient, triadimenol, is a neurotoxic, triazole fungicide and is the subject of this risk assessment document. Triadimenol is also a major mammalian and plant metabolite of triadimefon, another neurotoxic triazole fungicide. The mode of toxic action for both triadimenol and triadimefon involves blocking the re-uptake of dopamine which leads to increased motor activity and hyperactivity in rodents. These pesticides act as indirect dopamine agonists by binding to the dopamine transporter and increasing levels of synaptic dopamine.

Triazole fungicide pesticides, in general, are believed to exhibit their fungicidal activity through an inhibition of ergosterol biosynthesis, leading to an inhibition of cell wall percursors. Crofton (1996) evaluated the potential for 14 triazole fungicides and structurally related compounds. The purpose was to screen these compounds to determine whether central nervous system toxicity, particularly increased motor activity, is characteristic of other triazole fungicides. Crofton (1996) showed that of the chemicals tested, only triadimefon and triadimenol were able to induce hyperactivity; none of the other triazoles or related compounds tested produced this effect. The author hypothesized that the ether oxygen component of the triadimenol and triadimefon molecules appears to be an important structural requirement for induction of hyperactivity in rats. As such, at this time, although the fungicidal activity of triadimefon and triadimenol may be through the inhibition of sterol synthesis, the primary mode of toxicity in mammals appears to be neurotoxicity mediated through an indirect monoaminergic mechanism that appears to be specific to triadimefon and triadimenol only.

4.2.2 Toxicological Effects

As mentioned above, triadimenol is known to cause neurotoxic effects. In a central nervous effects study in mice (MRID 00145083), neurotoxicity was observed when KWG 0519 (Triadimenol) at doses ranging from3.75 to 60 mg/kg stimulated spontaneous mobility, increased irritability and escape response and augmented certain reflexes. In addition, doses of 15 and 60 mg/kg potentiated the effect of amphetamine while doses of 12 to 48 mg/kg antagonized the reserpin response. Triadimenol also prolonged the hexobartital sleeping time at 15 and 60 mg/kg. Similarly, rats exposed to 48 mg/kg triadimenol elicited an excitatory effect. A comparison with caffeine (doses of 2.5 and 10 mg/kg) showed that the effect of 2.5 mg/kg caffeine corresponded approximately to that of 12 to 15 mg/kg KWG 0519, in the amphetamine potentiation test 2.5 mg/kg caffeine elicited a similar response as 4 mg/kg KWG 0519, while in the antagonism of ptosis 10 mg/kg caffeine and 12 mg/kg KWG 0519 were comparable. The no- effect dose was 1 mg/kg for caffeine. The findings of this study point to a potential for stimulation of Central Nervous System (CNS).

In addition, following exposure to triadimefon, acute neurotoxic signs observed in mice, rats, and rabbits consisted of "apathy, labored breathing, increased/ decrease mobility, staggering and cramped posture, aggressiveness, and self- mutilation" (MRID 00149331). The formulation Bayleton 50% Wettable Powder, has been shown to cause hyperactivity, biting and antagonism behavior in rats, and the durations of these effects were dose- related. (Mobay Report No. 88, submitted in FIFRA 88, Phase III). Baytan (triadimenol), the major metabolite of triadimefon, is also known to cause CNS- related excitatory effects in rats and mice [(from the memo dated February 27, 1992: Triadimefon. Section 18, Reissuance of Emergency Exemption for the use of Bayleton 50% Dry Flowable Fungicide (EPA Reg. No. 3125-320) to control powdery mildew on artichokes in the state of California)]).

The neurotoxic endpoint seen with triadimefon and triadimenol is supported by the results of numerous studies reported in the open literature. In fact, the motor behavior stimulant effect of triadimefon has been sufficiently characterized such that the compound was used as a prototype in an interlaboratory comparison of behavioral toxicology methods (Crofton *et al.*, 1991; Moser and MacPhail, 1992). In addition, triadimefon is used in contract laboratories as a positive control for motor activity in adults animals (Crofton et al, 2004). Doses of triadimefon (50-100 mg/kg) have been reported to increase locomotion and rearing in rats (Walker *et al.*, 1990). The highest dose of triadimefon tested in this study (200 mg/kg) induced three stereotypic behaviors: head weaving, circling, and backward locomotion (Walker et al., 1990). Crofton *et al.* (1991) reported hyperactivity in rats following oral exposure to triadimefon with LOAELs ranging from 50 to 100 mg/kg. Walker and Mailman (1996) reported that acute administration of triadimefon and triadimenol resulted in a neurotoxic syndrome in rats characterized by increased motor

activity, stereotyped behaviors, and altered monamine metabolism.

To reiterate, the endpoint of concern is neurotoxicity seen after acute exposure to both triadimefon and triadimenol. Upon reviewing the toxicological database for the fungicidally active ingredient triadimenol, it is noted that the CNS study (MRID 00145083) was not a comprehensive study and the primary reason for conducting it was to establish whether the compound had a centrally stimulating effect. Based on the available data on the similar structure, effects and mode of action of triadimefon and triadimenol, the current triadimefon neurotoxicity data (ACN and SCN) will be used to establish the triadimenol acute and chronic reference doses.

As described below, NOAELs and LOAELs for both acute and subchronic (90 day) exposures in guideline studies are similar, suggesting that the neurotoxicity resulting from exposure to triadimefon does not accumulate. Similarly, no accumulation of toxicity was observed in studies by Crofton *et al.* (1988) and Moser *et al.* (1995) following seven and 14 days of exposure, respectively. Further evidence is also provided by Ikaiddi *et al.* (1997) who showed lack of accumulation of neurotoxicity following 14 days of dosing with some tolerance on aminergic endpoints. The Agency notes that the dose spacing between the NOAEL and LOAELs in the guideline acute and subchronic neurotoxicity studies are fairly large (>10-fold). This large dose spacing may contribute to the conservative nature of the current risk assessment. As the Agency refines its preliminary risk assessment for triadimenol in the coming months, dose-response studies from the literature may provide additional information for the hazard characterization of triadimenol.

In the available chronic studies, FOBs and motor activity were not measured and as such, hyperactivity was generally not observed. Liver toxicity was noted in subchronic (dog and rats) and chronic (rats, mice, and dogs) studies. Specifically, changes in liver enzymes were noted in the chronic dog and mouse studies. Changes in liver weights were noted in dog and rat subchronic studies. Increased incidence of hepatocellular hypertrophy in both sexes were noted in rats.

4.2.3 Dose-Response

Acute neurotoxicity: In an acute oral neurotoxicity study (MRID 43936101), twelve Wistar (Hsd Win:WU) rats/sex/group were dosed by gavage with nominal dose of 0, 2, 35, 450 (females only), or 600 (males only) mg/kg of **triadimefon** (MEB 6447; 95.8% a.i.; Lot No.: 203480004) in polyethylene glycol 400 (5 mL/kg). Analytically confirmed doses were 0, 2, 31.2, 424.4 (females only) and 587.4 (males only). The animals were monitored for a 14-day observation period. All twelve rats/sex/group were tested in the functional observational battery (FOB) and motor activity (MA) measurements, and six rats/sex/group were perfused for neuropathology.

Within two days after dosing, one high-dose male and four high-dose females died. Clinical signs were observed in the mid- and high-dose males and high-dose females. Mid- dose males exhibited moderate hyperactivity. High dose rats showed signs of severe hyperactivity,

stereotypic behavior, self-mutilation, diarrhea, and increased rearing. Decreased body weights were observed on Day 7 in high-dose males (-7.6%; $p<0.05$) and females (-4.5%; n.s.).

Dose-related effects were observed in the Functional Operational Battery in mid- and high-dose males and females. On day 0, hyperactivity was indicated by affected posture and gait, increased mobility, searching and cleaning gestures, stereotypy, increased arousal, and increased open field rearing incidence. Hyperactivity, indicated by an increased incidence of open field rearing, was still observed at day 7 or day 14 in mid- or high-dose males, respectively. In mid-dose females, rearings were increased at day 7 with complete reversibility at day 14. Body temperatures were significantly ($p<0.05$) increased in high-dose males and females compared to controls.

Grip strength was marginally decreased in high-dose males and females on days 7 and 14 (males only). Hindlimb foot splay was decreased in high-dose males on days 0 and 7. Functional Operational Battery effects were completely reversible until the end of the study in females and largely reversible in males.

On day 0, mid- and high-dose males and females exhibited statistically significant increases (226.9-317.5%) in motor activity. On day 7, mid-dose males still had a statistically significant increase (33.6%) in motor activity (interval 50-60 minutes), while a nonstatistically significant increase (26.2%) was present on day 14 (intervals 30-60 minutes). Mid-dose females exhibited marginal increases in motor activity on days 7(46.7%) and 14 (34.2%).

Statistically significant increases (326.7-485.6%) in locomotor activity were observed in mid- and high-dose males and females on day 0 persisting until the end of the study period (Day 14) though to a lesser extent (28.1- 50.2%). Statistically significantly decreased habituation was noted in mid- and high-dose the males and females on day 0. This continued to a smaller degree for mid-dose males and females on day 7 and for mid- and high-dose males on day 14. The blind alley and figure-eight activities were increased for mid- and high-dose males and females on day 0.

No effect on the absolute or relative brain weights was observed. No treatment-related gross effects or histopathology were observed.

The LOAEL for systemic/neurobehavioral findings is 31.2 mg/kg based on clinical signs, FOB, rearing, body temperature, MA, habituation, and spatial distribution in males and females. The NOAEL is 2 mg/kg.

Subchronic neurotoxicity: In a subchronic neurotoxicity study (MRID 44153501), **triadimefon** (MEB 6477) technical (95.8-95.9% a.i.) was administered in the diet to 18 Wistar rats/sex/dose at levels of 0, 50, 800, or 2,200 ppm (0, 3.4, 54.6 and 149.8 mg/kg/day for males and 0, 4.3, 68.7, and 189.7 mg/kg/day for females) for 13-weeks. Six rats/sex/dose level were subjected to neuropathological evaluations at the end of the exposure period and the remaining 12 rats/sex/dose level were observed for another 4 (males) or 10 (females) weeks to investigate the

persistence of the toxicological effects.

At 800 ppm (54.6♂ and 68.7♀ mg/kg/day) there were increases in rearing (both sexes) and motor and locomotor activity (females only) and other indications of hyperactivity especially in females including clinical signs (mobility, digging, and spilling food and water); body weight and weight gain were also decreased (9% ♂ and 14% ♀) in both sexes in the initial four weeks of dosing. There were also slight (not statistical significant) increases in male brain relative weight and grip strength. At 2200 ppm (149.8♂ and 189.7♀ mg/kg/day) there was stereotypy (pacing only in a few rats), and increased relative brain weight (18% both sexes). Increased landing foot splay and grip strength were also evident. The effects were considered slowly reversible, however, there was some evidence of hyperactivity persisting. The LOAEL for neurotoxicity is 800 ppm (54.6♂ and 68.7♀ mg/kg/day) based largely on hyperactivity. The NOAEL is 50 ppm (3.4♂ and 4.3♀ mg/kg/day).

Similar signs / effects were seen in the triadimefon developmental toxicity study (MRID 00089023) where the maternal NOAEL is 10 mg/kg/day and the LOAEL is 50 mg/kg/day based on dose- related increase in both degree and duration of motor activity and/ or depression of maternal weight.

Additional Information from Literature Sources:

1) Crofton, KM., Boncek, VM., and Reiter, LW. 1988. Hyperactivity induced by triadimefon, a triazole fungicide. *Fundam. Appl. Toxicol.* 10, 459-465.

2) Crofton, KM., Boncek, VM., and MacPhail, RC. 1989. Evidence for monoaminergic involvement in triadimefon - induced hyperactivity, *Psychopharmacology* 97, 326-330.

3) Moser, VC and MacPhail, RC. 1989. Neurobehavioral effects of triadimefon, a triazole fungicide, in male and female rats. *Neurotoxicol. Teratol.* 11, 285-293.

4) Crofton, KM., Howard, JL., Moser, VC., Gill, MW., et al. 1991. Interlaboratory comparison of motor activity experiments: implications for neurotoxicological assessments. *Neurotoxicol. Teratol.* 13 (6): 599- 609.

5) Moser, VC and MacPhail, RC. 1992. International validation of the neurobehavioral screening battery: The IPCS/WHO collaborative study. *Toxicol. Lett.* 64-65 Spec. No., 217-223.

6) Moser, VC., Cheek, BM., and MacPhail, RC. 1995. A multidisciplinary approach to toxicological screenings: III. Neurobehavioral toxicity. *Journal Toxicol Environ Health* Jun 45(2): 173-210.

7) Crofton, KM. 1996. A structure- activity relationship for the neurotoxicity of triazole

fungicites. *Toxicol. Lett* 84 (3): 155-159.

8) Walker, QD and Mailman, RB. 1996. Triadimefon and triadimenol: effects on monoamine uptake and release. *Toxicol. Appl. Pharmacol.* 139 (2): 227- 233.

9) Ikaiddi, MU., Akunne, HC., and Soliman, KE. 1997. Behavioral and neurochemical effects of acute and repeated administration of triadimefon in the male rat. *Neurotoxicology* 18(3): 771-80.

10) Crofton, KM., Makris, SL., Sette, WF., Mendez, E., and Raffaele, KC. 2004. A qualitative retrospective analysis of positive control data in developmental neurotoxicity studies. *Neurotoxicology and Teratology* 26; 345-352.

4.2.4 Developmental Toxicity Studies

Rabbit Developmental: In a developmental toxicity study (MRID 40307805), triadimenol (97% a.i.) was administered in 0.5% Cremophor EL orally, via gavage, in a dosing volume of 4 mL/kg, to 16 female Chinchilla rabbits/group, at dose levels of 0, 8, 40, or 200 mg/kg/day, on gestation days (GD) 6 through 18. All surviving does were sacrificed on GD 28 and their fetuses were removed by cesarean and examined.

When compared to concurrent controls, no treatment-related changes were observed in maternal mortality, the number of live and dead fetuses, fetal weights, or maternal pathology. At 200 mg/kg, all does appeared excited approximately 30 minutes post-dosing from GD 10 until study termination. In addition, several animals in this group suffered a loss of hair on the forepaws and toes. Decreased ($p<=0.05$) body weights were noted in the 200 mg/kg does during GDs 7-24 (decr. 7-14%). In addition, mean maternal food consumption was decreased ($p<=0.05$) in these animals during GDs 6-19 (decr. 22-61%), with the greatest decreases occurring at dose initiation. Increased post-implantation loss (12.8% treated vs. 3.8 % controls) and early resorptions per doe (0.7 treated vs. 0.1 controls) were observed at 200 mg/kg. Neither of these cesarean findings was statistically significant.

The maternal LOAEL is 200 mg/kg/day based on clinical signs of toxicity, decreased body weights and food consumption. The maternal NOAEL is 40 mg/kg/day. At 200 mg/kg, the number of fetuses (7/95 treated vs. 0/128 controls) and litters (6/14 treated vs. 0/16 controls) affected with skeletal abnormalities was greater ($p<=0.01$) than controls. These abnormalities involved rib, vertebral, and/or sternal elements. The developmental toxicity LOAEL is 200 mg/kg based on skeletal abnormalities and increased post- implantation loss and early resorptions. The developmental toxicity NOAEL is 40 mg/kg/day.

Prenatal Developmental / Rat: In a prenatal developmental toxicity study (MRIDs 40307804

and 40887702), Baytan (triadimenol; 97% a.i., Lot/Batch # 203 519 123) in 0.5% (w/v) aqueous Cremophor EL was administered to pregnant Wistar/HAN, Kfm: WIST outbred, SPF rats (25/dose) via gavage in a dosing volume of 10 mL/kg at concentrations of 0, 30, 60, or 120 mg/kg/day on GDs 6 through 15. All dams were sacrificed on GD 21 and their uterine contents examined.

There were no unscheduled deaths during the study. When compared to concurrent controls, there were no effects of treatment on maternal clinical observations, gross pathology, numbers of dead fetuses, sex ratios, or fetal weights. Maternal body weights were significantly decreased during GDs 8-17 at 60 mg/kg and GDs 7-18 at 120 mg/kg. Body weight gains were decreased during dosing in the 60 mg/kg (decr. 6-14%) and 120 mg/kg (decr. 15-41%) dams. Corrected (for gravid uterine weight) body weight gains were decreased (decr. 23%; not significant) in the 120 mg/kg dams. Food consumption was significantly decreased during treatment in the 60 mg/kg (decr. 6-11%) and 120 mg/kg (decr. 8-20%) dams. The mean number of resorptions was increased from 0.8 in controls to 1.5 at 120 mg/kg. Likewise, the percent post-implantation loss was increased in this group (11.8% treated vs 5.9% controls).

The maternal LOAEL is 60 mg/kg/day based on decreased body weights, body weight gains, and food consumption. The maternal NOAEL is 30 mg/kg/day. Dose-dependent increases ($p<=0.01$) in fetal and litter incidences of supernumerary ribs were observed at 60 and 120 mg/kg/day.

The following information was taken from the memorandum (TXR# 007290): "The issue of supernumerary ribs was discussed with L. Chitlik (HED) on several occasions in April and May 1989. In a meeting between R. Engler (HED) and L. Chitlik on May 4, 1989, it was concluded that 30 mg/kg/day may be a threshold for this variation because of the apparent trend. Furthermore, in TXR#007290 it was indicated that the low dose concern may not just be limited to supernumerary ribs. Therefore, a definite NOAEL could not be established for developmental toxicity, and consequently the study was classified as Core Supplementary. The registrant is requested to submit a new teratogenicity study in the same strain of rats to define the NOAEL for the developmental toxicity."

A subsequent developmental toxicity study in the rat (MRID 41498401; TXR# 008269 & 009704), conducted in 1990, was submitted, reviewed, and found acceptable with a LOAEL of 60 mg/kg/day based on supernumerary ribs and a NOAEL of 25 mg/kg/day. The developmental LOAEL is 60 mg/kg/day based on increased incidences of supernumerary ribs. The developmental NOAEL is 30 mg/kg/day.

Prenatal Developmental/Rat: In a prenatal developmental toxicity study (MRID 41498401), Baytan (triadimenol; 95% a.i., Lot/Batch # 6-03-0140) in 0.5% (w/v) aqueous carboxymethylcellulose and 0.4% (w/v) aqueous Tween 80 NF was administered to pregnant Crl:CD BR rats (28/dose) via gavage in a dosing volume of 10 mL/kg at concentrations of 0, 5, 15, 25, or 60 mg/kg/day on gestation days (GDs) 6 through 15. All dams were sacrificed on GD 20 and their uterine contents examined.

There were no unscheduled deaths during the study. When compared to concurrent controls, there were no effects of treatment on maternal clinical observations, clinical chemistry, liver weights, gross pathology, numbers of abortions, live or dead fetuses, resorptions, sex ratio, or fetal weight. Maternal body weights were decreased (decr. 13-24%; p<=0.05) during dosing (GDs 6-16) in the 15, 25, and 60 mg/kg dams. Likewise, adjusted (for gravid uterine weight) body weight gains were decreased in the 15 (decr. 16%; p<=0.01), 25 (decr. 9%; not significant), and 60 (decr. 22%; p<=0.01) mg/kg dams. The lack of statistical significance at 25 mg/kg is likely due to the inclusion of data from dam #1862, which had only one implant and a uterine weight of only 7.7 grams. A transient decrease (p<=0.05) in food consumption was observed on day 7 in the 15 and 60 mg/kg dams. Placental weight was increased (incr. 21%; p<=0.01) at 60 mg/kg.

The maternal LOAEL is 15 mg/kg/day based on decreased body weights and adjusted (for gravid uterine weight) body weight gains. The maternal NOAEL is 5 mg/kg/day. The incidence of extra ribs, a variation, was increased (p<=0.01) at 60 mg/kg/day (21.2% fetal incidence; 71.4% litter incidence) compared to concurrent controls (0.5% fetal incidence; 3.6% litter incidence). Incidences of this variation exceeded historical controls (0.5-18.6% fetal incidence; 3.7-65.2% litter incidence). The developmental LOAEL is 60 mg/kg/day based on increased incidences of extra ribs, a variation. The developmental NOAEL is 25 mg/kg/day.

Prenatal Developmental / Rabbit: In a prenatal developmental toxicity study (MRID 42365001), Baytan (triadimenol; 96.0% a.i., Lot/Batch #PF8741) in 0.5% (w/v) aqueous carboxymethyl-cellulose and 0.4% (w/v) aqueous Tween 80 NF was administered to pregnant New Zealand White rabbits (20/dose) via gavage in a dosing volume of 5 mL/kg at concentrations of 0, 5, 25, or 125 mg/kg/day on gestation days (GDs) 6 through 18. All does were sacrificed at the end of the exposure period and their uterine contents examined.

There were no unscheduled deaths during the study. When compared to concurrent controls, there were no effects of treatment on maternal clinical signs, liver enzymes, liver weights, gross pathology, litter size, numbers of live fetuses, dead fetuses, or resorptions, post-implantation loss, sex ratio, fetal weight, or placental weight. Mean litter size was decreased in the 25 mg/kg (decr. 32%) and 125 mg/kg (decr. 26%). However, the decreased in litter size was due to decreases in the numbers of corpora lutea (19-20%) and, thus, implantations (decr. 25-32%) in these groups occurring prior to initiation of treatment.

At 125 mg/kg/day, maternal body weights were decreased (decr. 6%; p<=0.05) during GDs 13-16. Body weight gains were decreased during the dosing period, GDs 6-18, (-0.07 kg treated vs 0.12 kg in controls; p<=0.01) and for the entire gestation period (decr. 29%; p<=0.05). Food consumption was decreased (p<=0.05) on GDs 7 (decr. 6%), 12 (decr. 26%), and 15 (decr. 24%).

The maternal LOAEL is 125 mg/kg/day based on decreased body weights, body weight gains, and food consumption. The maternal NOAEL is 25 mg/kg/day. The developmental LOAEL was

not observed. The developmental NOAEL is 125 mg/kg/day (HDT). Increased fetal ($p<=0.05$) and litter (not significant) incidences of the following skeletal findings were observed in the 125 mg/kg fetuses compared to concurrent controls: (i) incomplete ossification of the skull; (ii) enlarged fontanelle in the skull; (iii) presence of calcified body on the skull; (iv) irregular spinous process on the scapula; and (v) incomplete ossification of the posterior phalanges.

4.2.5 Reproductive Toxicity Studies

In a two-generation reproduction toxicity study (MRID 00151248) triadimenol; 97.5% a.i.) was administered continuously in the diet to SPF rats (10 males and 20 females/dose) at nominal dose levels of 0, 20, 100, or 500 ppm (0,1,5, or 25 mg/kg/day). The P parental animals were given test diets for approximately 10 weeks before they were mated to produce the F1a litters. Two weeks after their litters were weaned, the P animals were mated for a second time to produce the F1b litters. The F1b parental animals were randomly selected to become the parents of the F2 generation 5 days after birth. Following weaning, the F1a parents received the test diets for approximately 12 weeks before they were mated to produce the F2a and F2b litters. The F1a, F2a, and F2b litters were weaned after four weeks and then sacrificed.

Mortality, clinical signs, gross pathology, and histopathology in the parental animals and their offspring were unaffected by treatment. Additionally, parental food consumption (premating), reproductive performance, and organ weights were not affected by treatment. Reproductive function, sexual maturation, and pup organ weights were not evaluated. At 25 mg/kg/day in the F1b generation, body weights were slightly decreased ($p<=0.05$) during premating week 15 in the males and during most of premating in the females (decr. 6-8%). During gestation, body weights were decreased ($p<=0.05$) during GDs1-6 of the first mating and GDs 1-15 of the second mating (decr. 8-10%). During lactation, body weights were decreased ($p<=0.05$) during LDs 14-21 of the first mating and LDs 7-21 of the second mating (decr. 6-10%). Body weight gains during lactation were decreased for both matings (decr. 32-50%). No treatment-related findings were noted at the 1 or 5 mg/kg/day dose levels.

The LOAEL for parental toxicity is 25 mg/kg/day based on decreased body weights and body weight gains in the F1b generation. The NOAEL is 5 mg/kg/day. At 25 mg/kg/day, decreased ($p<=0.05$) pup weights were observed in the F1a and F1b litters during early lactation and in the F2a litters during late lactation (decr. 12-18%). No treatment-related findings were noted at 1 or 5 mg/kg/day dose levels.

The LOAEL for offspring toxicity is 25 mg/kg/day based on decreased pup weight. The NOAEL is 5 mg/kg/day. This study was classified acceptable/ guideline.

4.2.6 Pre-and/or Postnatal Toxicity

There was no evidence for quantitative and qualitative susceptibility following oral or dermal exposures to rats *in utero* or oral exposure to rabbits *in utero*. The degree of concern for pre-

and/or post-natal susceptibility is low because the rabbit NOAEL (20 mg/kg/day) is adequate due to dose spacing. The endpoint used for risk assessment purposes (NOAEL of 3.4 mg/kg/day from the subchronic neurotoxicity study) is 10x lower than the rabbit NOAEL and it is accounted for in the overall FQPA database uncertainty factor of 10x for the lack of a DNT.

4.3 Recommendation for a Developmental Neurotoxicity Study

The mode of toxic action for triadimenol involves blocking the re-uptake of dopamine. These pesticides act as indirect dopamine agonists by binding to the dopamine transporter and increasing levels of synaptic dopamine. The toxicological impact of blocking this re-uptake following exposure to triadimenol during development is not known. A developmental neurotoxicity study with triadimenol is not required at this time, pending the outcome of an acute and/or subchronic neurotoxicity study(ies).

4.4 Special FQPA Safety Factor(s) Required and Rationale

Based on the above data, the special FQPA safety factor of 10x is not required since the current developmental and reproductive toxicity studies do not suggest that the young are more sensitive than adult animals, and the lack of a DNT is addressed by the FQPA database uncertainty factor of 10x. Therefore, the FQPA Safety Factor is 1x.

4.5 Hazard Identification and Toxicity Endpoint Selection

4.5.1 Acute Reference Dose (aRfD) - General Population

No appropriate acute endpoint could be determined from the **triadimenol** database (see Section 4.2.1). Therefore, the **Triadimefon** subchronic neurotoxicity study in rats (MRID 44153501) was chosen for the acute Reference Dose (aRfD). Triadimefon (MEB 6477) technical (95.8-95.9% a.i.) was administered in the diet to 18 Wistar rats/sex/dose at levels of 0, 50, 800, or 2,200 ppm (0, 3.4, 54.6 and 149.8 mg/kg/day for males and 0, 4.3, 68.7, and 189.7 mg/kg/day for females) for 13 weeks. Six rats/sex/dose level were subjected to neuropathological evaluations at the end of the exposure period and the remaining 12 rats/sex/dose level were observed for another 4 (males) or 10 (females) weeks to investigate the persistence of the toxicological effects.

At 800 ppm (54.6♂ and 68.7♀ mg/kg/day) there were increases in rearing (both sexes) and motor and locomotor activity (females only), as well as other indications of hyperactivity (especially in females). Indications of hyperactivity include clinical signs (motility, digging, spilling food and water); body weight and body weight gain (9% ♂ and 14% ♀) were also decreased in both sexes in the initial four weeks of dosing. There were also slight (not significant) increases in male brain relative weight and grip strength.

At 2200 ppm (149.8♂ and 189.7♀ mg/kg/day) there was stereotypy (pacing only in a few rats),

relative brain weight (18% both sexes) and increased frequency and intensity of the symptoms noted at 800 ppm. Increased landing foot splay and grip strength (believed to be associated with the decrease in body weight) were evident. The effects were considered slowly reversible since body weight recovered slowly and there was some evidence of hyperactivity persisting. The LOAEL for neurotoxicity is 800 ppm (54.6♂ and 68.7♀ mg/kg/day) based largely on hyperactivity. The NOAEL is 50 ppm (3.4♂ and 4.3♀ mg/kg/day).

For the acute dietary risk assessment, the Uncertainty Factor (UF) is 1000x: 10 x for interspecies extrapolation,10x for intraspecies variations, and 10x for FQPA database uncertainty (lack of an acute and/ or subchronic neurotoxicity studies).

$$\text{Acute RfD} = \frac{\text{3.4 mg/kg/day (NOAEL)}}{\text{1000 (UF)}} = 0.0034 \text{ mg/kg/day}$$

The **triadimefon** subchronic neurotoxicity study was used to established the aRfD, although an acceptable **triadimefon** acute neurotoxicity study is available. The endpoint of concern is neurotoxicity seen both after acute gavage and repeated dietary exposure. The clinical signs include increase rearing, motor activity, stereotypy, and self mutilation. It is noted that the acute neurotoxicity study NOAEL of 2 mg/kg/day is lower than the 3.4 NOAEL in the SCN selected for the overall risk assessment . The NOAEL of the ACN study appears to be an artifact of dose selection (large spacing between the doses i.e., 2, 31.2, 424.4 and 587.4 mg/kg); thus, use of the NOAEL of 3.4 mg/kg from the SCN is considered appropriate for this risk assessment.

Again, the Agency notes that the dose spacing between the NOAEL and LOAELs in the guideline acute and subchronic neurotoxicity studies are fairly large (>10-fold). This large dose spacing may contribute to the conservative nature of the current risk assessment. As the Agency refines its preliminary risk assessment for triadimenol in the coming months, dose-response studies from the literature may provide additional information for the hazard characterization of triadimenol.

4.5.2 Chronic Reference Dose (cRfD)

The subchronic neurotoxicity study in rats (MRID 44153501) is chosen for the cRfD. Please see Section 4.5.1.

For the chronic dietary risk assessment, the Uncertainty Factor (UF) is as follows: 1000X (10x for interspecies extrapolation, 10x for intraspecies variations, and 10x for FQPA database uncertainty (lack of an acute and/ or subchronic neurotoxicity and inhalation studies).

$$\text{Chronic RfD} = \frac{\text{3.4 mg/kg/day (NOAEL)}}{\text{1000 (UF)}} = 0.0034 \text{ mg/kg/day}$$

The **triadimefon** subchronic neurotoxicity study was used to established the cRfD, although acceptable **triadimenol** chronic, reproductive, combined chronic/ carcinogenicity and carcinogenicity studies are available. Using the subchronic neurotoxicity study accounts for the most sensitive species and endpoints (rat vs. chronic dog study (MRID 00150484)). The endpoint of concern is neurotoxicity (SCN) and liver toxicity for the chronic studies. An extra factor will not be used for using a short-term factor (SCN) in a long- term risk assessment because the NOAEL available for the long- term studies (reproductive study MRID 00151248), carcinogenicity (MRIDs 00126259 and 00126260) and chronic (MRID 00150484) is higher than the NOAEL selected for this risk assessment (3.8 -19 mg/kg/day vs. 3.4 mg/kg/day).

4.5.3 Classification of Carcinogenic Potential

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the Cancer Assessment Review Committee (CARC) classified Triadmenol into the category C "possible human carcinogen." This classification is based on increased incidence of hepatocellular adenomas in females.

Table 9: Summary of Toxicological Doses and Endpoints

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (general population)	NOAEL = 3.4 mg/kg/day UF = 1000 Acute RfD = 0.0034 mg/kg/day	FQPA SF = 1X aPAD = acute RfD / FQPA SF = 0.0034 mg/kg/day	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Chronic Dietary (all populations)	NOAEL = 3.4 mg/kg/day UF = 1000 Acute RfD = 0.0034 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD / FQPA SF = 0.0034 mg/kg/day	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Cancer (oral, dermal, inhalation)	Classification: Category C "possible human carcinogen" based on increased incidence of hepatocellular adenomas in females.		

UF = Uncertainty Factor; FQPA SF = Special FQPA Safety Factor; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; PAD = population adjusted dose (a = acute, c = chronic); RfD = reference dose.
* Refer to Section 4.5

4.6 Endocrine Disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect

produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

5.0 PUBLIC HEALTH DATA

5.1 Incident Reports

For a review of human incident data for triadimenol and triadimefon, please refer to Section 9.0.

6.0 EXPOSURE CHARACTERIZATION / ASSESSMENT

6.1 Dietary Exposure / Risk Pathway

6.1.1 Residue Profile

Tolerances are established for residues of triadimenol and its butanediol metabolite, 4-(4-chlorophenoxy)-2,2-dimethyl-4-(1H-1,2,4-triazol-1-yl)-1,3-butanediol] (calculated as triadimenol) in/on various plant commodities [40 CFR §180.450(a)]. The established tolerances in plant commodities range from 0.01 (sorghum grain and fodder) to 2.5 ppm (green forage of oats, rye, and wheat). Tolerances are currently established for residues of triadimenol and its metabolites containing the chlorophenoxy moiety (calculated as triadimenol) in livestock commodities at 0.01 ppm (milk and poultry commodities) and 0.1 ppm (fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep).

Triadimenol and its butanediol metabolite (KWG 1342) are also regulated as metabolites of the fungicide triadimefon (40 CFR §180.410). In addition, 40 CFR §180.3(d)(13) specifies that where tolerances are established for residues of both 1-(4- chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone (triadimefon) and triadimenol including its butanediol metabolite, 4-(4-chlorophenoxy)-2,2-dimethyl-4-(1H-1,2,4-triazol-1-yl)-1,3-butanediol (KWG 1342), in or on the same raw agricultural commodity and its products thereof, the total amount of such residues shall not yield more residue than that permitted by the higher of the two tolerances. Currently, triadimefon and triadimenol do not share any uses, so 40 CFR §180.3(d)(13) should be deleted.

The reregistration requirements for plant metabolism have not been fulfilled. Two triadimenol specific metabolism studies (wheat and sugar beets) have recently been submitted and are currently under review by the Agency. Metabolism studies with triadimefon have been received and reviewed, and are used to determine residues of concern in/on apples, grapes, pears, pineapples, and raspberries. HED has examined the results of these studies and determined that the triadimefon residues of concern in/on apples, grapes, pears, pineapples, and raspberries for tolerance expression are triadimefon and triadimenol and for risk assessment are triadimefon, triadimenol, KWG 1323, and KWG 1342. Of these compounds, triadimenol and KWG 1342 are currently regulated in plant commodities.

HED has determined that translation of metabolism data from triadimefon to triadimenol is not appropriate for the existing uses on cereal grains and cotton. The metabolism studies with triadimefon were conducted using a foliar application whereas triadimenol is used only as a seed treatment. Additionally, in the submitted triadimenol seed treatment wheat study, residues in grain were not identifiable due to the low activity found in wheat grain. Therefore, HED concludes that the nature of the residue in cereal grains and cotton is not adequately understood; however, based on chemical structure and the probable metabolic pathway of triadimenol, the residues of concern for tolerance expression and risk assessment are likely to be triadimenol, KWG 1342, and KWG 1732 in/on cereal grains (barley, corn, oats, rye, and wheat) and cotton. Separate metabolism studies with triazole [^{14}C]- and phenyl [^{14}C]-labeled triadimenol applied as a seed treatment to corn or wheat and cotton should be conducted to confirm the residues of concern. The residues of concern for tolerance expression and risk assessment for bananas are triadimenol and KWG 1342.

Additionally, the Agency does have concern about the potential toxicity of 1,2,4-triazole and two conjugates, triazole alanine and triazole acetic acid, which are metabolites common to most of the triazole fungicides. To support the reassessment of existing tolerances and granting of new tolerances for parent triazole-derivative fungicide, EPA will be conducting separate human-health assessments reflecting aggregate exposure to 1,2,4-triazole.

The reregistration requirements for livestock metabolism are fulfilled based on acceptable goat and poultry metabolism studies submitted to support reregistration of triadimefon.

The Pesticide Analytical Manual (PAM) Vol. II does not contain a listing for triadimenol (February 1997 Index). However, the methods listed for triadimefon can be used for the determination of triadimenol, KWG 1323, KWG 1342, and KWG 1732. PAM lists two gas chromatographic methods with mass spectrometric detection (GC/MS) (Methods I and II) for the determination of triadimenol and its free and conjugated metabolites in plant and livestock commodities. Both methods are common moiety methods. The reported limit of quantitation (LOQ) is 0.05 and limit of detection (LOD) is 0.01 ppm for both methods.

In conjunction with triadimefon reregistration, Bayer has proposed a GC/MS method (Report No. 106549) for enforcement of tolerances for residues of triadimefon, triadimenol, KWG 1342,

KWG 1323, and KWG 1732 in/on barley, corn, cotton, oat, rye, and wheat commodities. The method has been successfully radiovalidated and has undergone independent laboratory validation. The reported method LOQ is 0.05 ppm for each analyte in cereal grains and 0.02 ppm in each analyte in cotton. Additionally, a GC method using a nitrogen/phosphorus detector (NPD; Report No. 80488) is available for determination of residues of triadimenol, KWG 1342, and KWG 1323 and is adequate for the enforcement of the banana tolerance. The method has undergone a successful Agency method validation on tomatoes and was submitted to the FDA for publication in PAM Vol. II. The reported method LOQ is 0.01 ppm for each analyte.

The reregistration requirements for multiresidue method testing for residues of triadimenol, KWG 1342, and KWG 1732 are satisfied.

The reregistration requirements for storage stability data are not satisfied for field corn, sweet corn, cotton, and wheat forage, hay, straw, and processed commodities pending the results from the requested metabolism studies.

The reregistration requirements for data depicting the magnitude of triadimenol residues of concern in meat, milk, poultry, and eggs have been fulfilled. Acceptable ruminant and poultry feeding studies have been submitted and evaluated. Triadimenol is not registered for use as a direct livestock treatment. The nature of the residue in livestock is adequately defined for the current uses. HED concludes that the supported uses on barley, corn, cotton, oats, rye, and wheat result in a 40 CFR §180.6(a)(3) situation for ruminant commodities; i.e., there is no reasonable expectation of finite residues in ruminant commodities. Therefore, additional data on the transfer of residues to meat, milk, poultry, and eggs are not required and all tolerances for triadimenol residues in livestock commodities should be revoked pending results from the requested corn and wheat metabolism studies. If foliar uses or registration on additional major livestock feed items are requested, then triazole and phenyl-labeled livestock metabolism studies would be required. Such data may, in turn, trigger the need for magnitude of the residue (feeding) studies in livestock.

The reregistration requirements for magnitude of the residue data in/on bananas are fulfilled. Additional field trials conducted with field corn (forage, grain, stover), sweet corn (forage, K+CWHR, grain, and stover), cotton (undelinted seed and gin byproducts), and wheat (forage, grain, hay, and straw) are required pending the results from the requested metabolism studies.

The reregistration requirements for magnitude of the residue in the processed commodities of field corn and cotton have been fulfilled. A wheat processing study conducted with triadimenol applied to wheat as a seed treatment should be submitted once the requested wheat metabolism studies have been submitted and reviewed.

No data pertaining to confined/field accumulation of triadimenol residues in rotational crops have been submitted; however, confined rotational crop data for triadimefon have been submitted and translated. The reregistration requirements for accumulation in rotational crops are fulfilled,

pending submission of the requested corn or wheat and corn and cotton triazole labeled metabolism studies for final determination of the metabolites of concern. HED has concluded that limited field rotational crop studies for triadimenol must be submitted.

A general summary of residue chemistry deficiencies are listed below.

Regulatory Recommendations and Residue Chemistry Deficiencies

- Separate metabolism studies with triazole-^{14}C and phenyl-^{14}C labeled triadimenol applied as a seed treatment to wheat and corn should be conducted to confirm the residues of concern.

- Storage stability data for triadimenol, KWG 1342, and KWG 1732 in/on field corn, sweet corn, cotton, and wheat processed commodities are required pending the results from the requested metabolism studies. Storage stability data for KWG 1732 in/on wheat forage, hay, and straw are required pending the results from the requested metabolism studies.

- Crop field trial data depicting residues of triadimenol, KWG 1342, and KWG 1732 in/on field corn (forage, grain, stover), sweet corn (forage, K+CWHR, grain, and stover), cotton (undelinted seed and gin byproducts), and wheat (forage, grain, hay, and straw) grown from seed treated at the maximum rate are required pending the results from the requested metabolism studies.

- A wheat processing study conducted with triadimenol applied to wheat as a seed treatment should be submitted once the requested corn or wheat metabolism studies have been submitted and reviewed.

- Limited field rotational crop studies for triadimenol must be submitted pending the results from the requested metabolism studies.

6.1.2 Tolerance Reassessment Summary

A summary of the triadimenol tolerance reassessment and recommended modifications in commodity definitions is presented in the following table:

Table 10: Tolerance Reassessment Summary for Triadimenol.

Commodity	Current Tolerance, ppm	Reassessed Tolerance, ppm	Comment *[Correct Commodity Definition]*
Tolerances Established Under 40 CFR §180.450 (a)			
Banana (whole)[1]	0.2	0.2	

Table 10. Tolerance Reassessment Summary for Triadimenol.			
Commodity	Current Tolerance, ppm	Reassessed Tolerance, ppm	Comment *[Correct Commodity Definition]*
Barley, grain	0.05	TBD[2]	
Barley, straw	0.2	TBD	
Corn, forage	0.05	TBD	*[Corn, field, forage]* *[Corn, sweet, forage]*
Corn, fresh (including sweet), (K+CWHR)	0.05	TBD	*[Corn, sweet, K+CWHR]*
Corn, grain	0.05	TBD	*[Corn, field, grain]* *[Corn, pop, grain]*
Corn, stover	0.05	TBD	*[Corn, field, stover]* *[Corn, pop, stover]* *[Corn, sweet, stover]*
Cotton, forage	0.02	Revoke	No longer considered a significant livestock feed item.
Cotton, undelinted seed	0.02	TBD	
Oat, forage	2.5	TBD	
Oat, grain	0.05	TBD	
Oat, straw	0.2	TBD	
Rye, forage	2.5	TBD	
Rye, grain	0.05	TBD	
Rye, straw	0.1	TBD	
Sorghum, forage, hay	0.05	Revoke	Bayer does not intend to support use of triadimenol on sorghum.
Sorghum, grain	0.01	Revoke	Bayer does not intend to support use of triadimenol on sorghum.
Sorghum, grain, stover	0.01	Revoke	Bayer does not intend to support use of triadimenol on sorghum.
Wheat, forage	2.5	TBD	
Wheat, grain	0.05	TBD	
Wheat, straw	0.2	TBD	

Table 10: Tolerance Reassessment Summary for Triadimenol			
Commodity	Current Tolerance, ppm	Reassessed Tolerance, ppm	Comment *[Correct Commodity Definition]*
Tolerances Established Under 40 CFR §180.450 (b)			
Cattle, fat	0.1	Revoke	The available data indicate that tolerances for cattle commodities are not required.
Cattle, meat	0.1		
Cattle, meat byproducts	0.1		
Egg	0.01	Revoke	The available data indicate that a tolerance for eggs is not required.
Goat, fat	0.1	Revoke	The available data indicate that tolerances for goat commodities are not required.
Goat, meat	0.1		
Goats, meat byproducts	0.1		
Hog, fat	0.1	Revoke	The available data indicate that tolerances for hog commodities are not required.
Hog, meat	0.1		
Hog, meat byproducts	0.1		
Horse, fat	0.1	Revoke	The available data indicate that tolerances for horse commodities are not required.
Horse, meat	0.1		
Horse, meat byproducts	0.1		
Milk	0.01	Revoke	The available data indicate that a tolerance for milk is not required.
Poultry, fat	0.01	Revoke	The available data indicate that tolerances for poultry commodities are not required.
Poultry, meat	0.01		
Poultry, meat byproducts	0.01		
Sheep, fat	0.1	Revoke	The available data indicate that tolerances for sheep commodities are not required.
Sheep, meat	0.1		
Sheep, meat byproducts	0.1		
Tolerances To Be Proposed Under 40 CFR §180.450 (a)			
Barley, hay	None established	TBD	
Cotton, gin byproducts	None established	TBD	
Oat, hay	None established	TBD	
Wheat, hay	None established	TBD	

1. 40 CFR §180.450(a) states that there are no U.S. registrations for banana (whole) as of 9/22/93.
2. TBD = To be determined.

Codex Harmonization

The Codex Alimentarius Commission (Codex) has established several maximum residue limits (MRLs) for triadimenol in/on various raw agricultural commodities. The Codex MRLs are expressed in terms of triadimenol *per se*. The MRLs have been established to accommodate triadimenol residues resulting from the use of triadimefon and/or triadimenol. Compatibility cannot be achieved with the Codex MRLs because these levels are expressed in terms of triadimenol only; the U.S. tolerances for plant commodities are expressed in terms of triadimenol, KWG 1342, and KWG 1732 in/on cereal grains and cotton and triadimenol and KWG 1342 in/on bananas. Additionally, all U.S. livestock tolerances should be revoked.

6.1.3 Acute and Chronic Dietary Exposure / Risk

Dietary risk for triadimenol is assessed by comparing acute (one-day) and chronic dietary exposure estimates (in mg/kg/day) to both the triadimenol aPAD and cPAD, with dietary risk expressed as a percentage of the aPAD and cPAD. Dietary risk is estimated for the general U.S. population and population sub-groups defined by sex, age, region, and ethnicity. The triadimenol aPAD (general population) and cPAD (all population subgroups) are both 0.0034 mg/kg bw/day, based on a NOAEL of 3.4 mg/kg bw/day and an uncertainty factor of 1,000X.

Acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.00 - 2.02), which incorporates consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods (as consumed) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment data are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) being considered is multiplied by the average daily consumption estimate for that food/food form. The resulting residue/consumption estimate for each food/food form is summed with the residue/consumption estimates for all other food/food

forms considered to arrive at a total (average) estimated exposure. Durations of chronic exposure vary from one-year as represented by "all infants," to lifetime exposure as represented by the general U.S. population, which combines all population subgroups to form a mean exposure value. It should be noted that all parameters of chronic dietary exposure estimates are averaged values (i.e. average food consumption, average residue, etc.). Dietary exposure estimates are also factored by the estimated weighted average usage, or "percent crop treated" data.

For acute exposure assessments, one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/ food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis.

Estimated Drinking Water Concentrations (EDWCs) are used directly in dietary exposure assessments to calculate aggregate dietary (food + water) risk. This is done by using the relevant model value as a residue for drinking water (all sources) in the dietary exposure assessment. The principal advantage of this approach is that the actual individual body weight and water consumption data from the CSFII are used, rather than assumed weights and consumption for broad age groups. This refinement has been used in estimating the dietary exposure component in the triadimenol aggregate risk assessment.

EDWCs are provided by OPP's Environmental Fate and Effects Division, and are incorporated into the following categories of the DEEM-FCID™ model: "water, direct, all sources" and "water, indirect, all sources." EDWCs for surface water are moderately refined, and calculated using the PRZM-EXAMS model. Estimated ground water concentrations for triadimenol are unrefined and are calculated using SCI-GROW; however, ground water concentrations were not used in this assessment as residues in ground water are lower than those in surface water.

EDWCs are calculated from the use of triadimenol as a seed treatment to wheat, corn, and cotton. The wheat scenario produced the highest concentrations and is used in this dietary assessment. For the acute assessment, the 30-year annual peak surface water concentration of 0.000393 ppm was used; for the chronic dietary assessment, the 1 in 10 year annual mean surface water concentration of 0.000194 ppm was used.

The acute dietary assessment utilizes anticipated residue estimates for bananas (based on available field trial data) and existing tolerance level residues for the remaining commodities. A default processing factor for dried bananas, available data from processing studies, and an assumption of 100% crop treated were also used in the assessment. For all supported commodities, the acute dietary risk estimates (food plus drinking water) do not exceed HED's level of concern at the 95th exposure percentile for the U.S. population (15% of the aPAD) and all

population subgroups. The highest exposed population subgroup is children 1-2 years of age, at 29% of the aPAD.

The chronic dietary assessment utilizes existing tolerance level residues, the default processing factor for dried bananas, available data from processing studies, and an assumption of 100% crop treated. For all supported commodities, the chronic dietary risk estimates (food plus drinking water) do not exceed HED's level of concern for the U.S. population (7% of the cPAD) and all population subgroups. The highest exposed population subgroup is children 1-2 years of age, at 23% of the cPAD. The results of the acute and chronic dietary exposure analysis are reported in the following table:

Table 11: Summary of Acute and Chronic Dietary (food + water) Exposure and Risk for Triadimenol

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000501	15	0.000251	7
All Infants (< 1 year old)	0.000798	23	0.000469	14
Children 1-2 years old	**0.000981**	**29**	**0.000770**	**23**
Children 3-5 years old	0.000871	26	0.000610	18
Children 6-12 years old	0.000639	19	0.000379	11
Youth 13-19 years old	0.000436	13	0.000224	7
Adults 20-49 years old	0.000329	10	0.000188	6
Adults 50+ years old	0.000249	7	0.000178	5
Females 13-49 years old	0.000318	9	0.000181	5

The **bolded** values represent the highest exposed populations for each of the risk assessments.

The acute and chronic dietary risk estimates from food only (not including drinking water) are presented in the following table, in order to illustrate the minimal contribution of drinking water to overall dietary risk from triadimenol:

Table 12: Summary of Acute and Chronic Dietary (food only) Exposure and Risk for Triadimenol.				
Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000494	15	0.000247	7
All Infants (< 1 year old)	0.000763	22	0.000456	13
Children 1-2 years old	**0.000961**	**28**	**0.000764**	**23**
Children 3-5 years old	0.000862	25	0.000604	18
Children 6-12 years old	0.000633	19	0.000375	11
Youth 13-19 years old	0.000428	13	0.000221	7
Adults 20-49 years old	0.000320	9	0.000185	5
Adults 50+ years old	0.000240	7	0.000174	5
Females 13-49 years old	0.000309	9	0.000177	5

7.0 AGGREGATE RISK ASSESSMENT

As part of the reregistration eligibility decision, the Agency is required by the Food Quality Protection Act to ensure *"that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there is reliable information."* As there are no residential uses associated with triadimenol, the aggregate risk assessment includes exposure from food and drinking water only. Acute and chronic aggregate risks (food + drinking water) are below HED's level of concern for all population subgroups.

Exposure to triadimenol can occur following the application of triadimenol as an active ingredient as well as from the metabolism/degradation of triadimefon. The current risk assessment only addresses the use of triadimenol as an active ingredient per se. Exposures from the pesticidal uses of triadimenol have not been aggregated with triadimenol exposures reflecting metabolism and/or degradation of triadimefon because risks attributable to uses of triadimefon already exceed HED's level of concern and because the resulting apparent increase in aggregate risk would unduly be associated with the registered uses of triadimenol. The Agency is soliciting comments on assumptions used in the current risk assessment. Should refinements be possible in the future, it may be appropriate to aggregate multiple routes and sources of exposures for these chemicals.

At this time the Agency has decided not to aggregate the exposures resulting from the independent use of these two chemicals. This decision not to aggregate was based on the risks

associated with the use of triadimefon, as the risk from triadimefon already exceed the Agency's level of concern by itself. Furthermore, the Agency feels that aggregating the metabolite triadimenol exposures from use of triadimefon with the exposures resulting from the use of triadimenol would not allow for the proper evaluation of the use of triadimenol active ingredient products. Should refinements be possible in the future, it may be possible and appropriate to aggregate multiple routes and sources of exposures for these chemicals.

8.0 CUMULATIVE RISK ASSESSMENT

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

9.0 HUMAN INCIDENT DATA REVIEW

The following data bases were consulted for the poisoning incident data on triadimefon/ triadimenol:

1) OPP Incident Data System (IDS): reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992.

2) Poison Control Centers: as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1998 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

There were nine reports of occupational exposure to triadimefon/triadimenol and 46 non-occupational exposures from 1993 through 2003. There were just two exposures reported from any type of exposure to triadimefon/triadimenol, but neither had medical outcome recorded or required medical care. Of the 46 non-occupational exposures, 13 occurred in children under six years of age. Of the total 20 cases with medically determined outcome, 11 reported minor medical outcome. Of the total 54 exposures to triadimefon/triadimenol, just four were seen in a health care facility and none required hospitalization. A review of symptoms revealed almost

exclusively irritation effects (including rash and erythema) to skin, mouth, throat, and eyes. These effects were reported a total of 24 times with some patients reporting two or more of these symptoms. There were four cases reporting headache and two reported cough. No other significant symptoms were reported.

3) California Department of Pesticide Regulation: California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

The majority of triadimefon/triadimenol incidents (92%) occurred prior to 1990. Most of the triadimefon/triadimenol cases (73%) involved use on grapes which is a labor intensive crop involving high exposure to foliar residues. Foliar residues accounted for half of the illnesses and nearly half of the systemic illnesses. Although most of the symptoms appeared to be minor, skin and eye irritation, and rash were among the most common topical symptoms. The most common systemic effects included nausea, headache, sneezing, congestion, difficulty breathing and other allergic-type reactions. There were three reports of vomiting.

4) National Pesticide Information Center (NPIC): NPIC is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

On the list of the top 200 chemicals for which NPIC received calls from 1984-1991 inclusively, triadimefon/triadimenol was not reported to be involved in human incidents.

5) National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) performs standardized surveillance in seven states from 1998 through 2002. States included in this reporting system are Arizona, California, Florida, Louisiana, Michigan, New York, Oregon, Texas, and Washington. Reporting is very uneven from state to state because of the varying cooperation from different sources of reporting (e.g., workers compensation, Poison Control Centers, emergency departments and hospitals, enforcement investigations, private physicians, etc.). Therefore, these reports should not be characterized as estimating the total magnitude of poisoning. The focus is on occupationally-related cases not residential or other non-occupational exposures. However, the information collected on each case is standardized and categorized according the certainty of the information collected and the severity of the case.

Out of 5,899 reported cases from 1998-2003, one involved triadimefon/triadimenol. However, this case was a duplicate of a California case included in the discussion above.

Conclusion: Both California and Poison Control Center data show a clear pattern of irritative, but usually minor symptoms from exposure to triadimefon/triadimenol. Irritation to skin, eyes, and respiratory passage occur readily among unprotected handlers (applicators and mixer/loaders) and among those who have substantial contact with foliage such as grape harvesters and tenders. It was unclear whether triadimefon/triadimenol might also be a sensitizer, contributing to allergic-type reactions.

10.0 DATA REQUIREMENTS

Product Chemistry:

- OPPTS Guideline 830.6313
- OPPTS Guideline 830.7000
- OPPTS Guideline 830.7050
- OPPTS Guideline 830.7550, 830.7560, or 830.7570
- OPPTS Guideline 830.7840 or 830.7860

Residue Chemistry:

- Separate metabolism studies with triazole-14C and phenyl-14C labeled triadimenol applied as a seed treatment to wheat and corn should be conducted to confirm residues of concern.
- Storage stability data for triadimenol, KWG 1342, and KWG 1732 in/on field corn, sweet corn, cotton, and wheat processed commodities are required pending the results from the requested metabolism studies. Storage stability data for KWG 1732 in/on wheat forage, hay, and straw are required pending the results from the requested metabolism studies.
- Crop field trial data depicting residues of triadimenol, KWG 1342, and KWG 1732 in/on field corn (forage, grain, stover), sweet corn (forage, K+CWHR, grain, and stover), cotton (undelinted seed and gin byproducts), and wheat (forage, grain, hay, and straw) grown from seed treated at the maximum rate are required pending the results from the requested metabolism studies.
- A wheat processing study conducted with triadimenol applied to wheat as a seed treatment should be submitted once the requested corn or wheat metabolism studies have been submitted and reviewed.
- Limited field rotational crop studies for triadimenol must be submitted pending the results from the requested metabolism studies.

Toxicology:

- Acute and subchronic neurotoxicity studies with triadimenol are required.

REFERENCES:

Samuel Ary. Triadimenol: Acute and Chronic Dietary Exposure Assessments for the Tolerance Reassessment Eligibility Decision (TRED) Document. DP Barcode D314928. November 18, 2005.

Samuel Ary. Triadimenol: Summary of Analytical Chemistry and Residue Data for the Tolerance Reassessment Eligibility Decision (TRED) Document. DP Barcode D314891. November 17, 2005.

Yvonne Barnes. Summary of Product Chemistry Data for Tolerance Reassessment (TRED) Document. DP Barcode D315152. November 22, 2005.

James Breithaupt. TRED for Triadimenol Drinking Water Assessment. DP Barcode D312519. February 9, 2005.

APPENDIX

The requirements (40 CFR 158.340) for food for Triadimenol are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	no	yes
870.3250	90-Day Dermal	no	no
870.3465	90-Day Inhalation	yes	no
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	no	no
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	no	no
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	no	no
870.6200b	90 Day Neuro. Screening Battery (rat)	no	no
870.6300	Develop. Neuro	no	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	no
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	n/a
	Subchronic Oral (rat)	no	n/a
	Six-month Oral (dog)	no	n/a

13544

R121796

Chemical: Triadimenol

PC Code: 127201
HED File Code: 14000 Risk Reviews
Memo Date: 2/9/2006
File ID: DPD326716
Accession #: 412-06-0013

HED Records Reference Center
2/27/2006