United States
Environmental Protection
Agency

Office of Pesticides
and Toxic Substances
(7501C)

PESTICIDE FACT SHEET

Name of Chemical: **FENHEXAMID**
Reason for Issuance: **New Chemical Registration**
Date Issued: **MAY 20, 1999**
Fact Sheet Number:

DESCRIPTION OF CHEMICAL

Chemical Name: N-(2,3-dichloro-4-hydroxyphenyl)-1-methyl cyclohexanecarboxamide

Common Name: Fenhexamid

Trade Names: Fenhexamid Technical (EPA Reg. No. 66330-GL)
Elevate 50 WDG (EPA Reg. No. 66330-GA)

EPA Chemical Code: 090209

Chemical Abstracts Service (CAS) Registry Number: 126833-17-8

Year of Initial Registration: 1999

Pesticide Type: Fungicide

Registrant: Tomen Agro, Inc.

U.S. Producer: Bayer AG, Agrochemicals Division

DESCRIPTION OF USE PATTERNS

The end-use product (Elevate 50 WDG) is a water dispersible granule formulation containing 50% active ingredient. The product is applied as a foliar spray by ground equipment only (no aerial application). The applications per season are as follows: Grapes (3 applications of 0.5 lb ai/A; Strawberries (4 applications of 0.75 lb ai/A; and Ornamentals 4-6 applications of 0.5-0.75 lb ai/A. The

maximum seasonal totals are 1.5 lbs ai/A for grapes, and 3.0 lbs ai/A for strawberries and ornamentals. The PHI is 0 days. The product is for commercial use only. There is a 30 day plant back restriction for all crops without a tolerance for fenhexamid.

SUMMARY OF SCIENCE FINDINGS

The Agency has reviewed toxicology, residue, environmental fate and effects data submitted by the TM-402 Task Force (comprised of Tomen Agro, Inc. and Bayer Corporation) to support the use fenhexamid for use on grapes, strawberries, and ornamentals. The data are considered to be adequate to ensure that use of the product for the registered purposes will cause no unreasonable adverse effects to man or the environment. Food Quality Protection Act considerations were included since there are food uses involved and surface and ground water could potentially be affected by use on food crops. The data used in this assessment are summarized below.

CHEMICAL CHARACTERISTICS

Color:	White powder
Empirical Formula:	$C_{14}H_{17}Cl_2NO_2$
Molecular Weight:	302.2
Physical State:	solid
Melting Point:	153° C
Vapor Pressure:	7 x 10^{-9} Torr (at 25° C)
Solubility in Water:	20 mg/L (ppm; at 20° C, pH 5-7)
Chemical Group:	Hydroxyanilide (new)

TOXICOLOGICAL CHARACTERISTICS

Acute Toxicity

Study Type	Technical Fenhexamid		Elevate 50% WDG	
	Results	Tox Category	Results	Tox Category
Acute Oral - Rats	M: LD_{50} >5000 mg/kg F: LD_{50} >5000 mg/kg	IV	M: LD_{50} >2000 mg/kg F: LD_{50} >2000 mg/kg	III
Acute Dermal - Rats	M: LD_{50} >5000 mg/kg F: LD_{50} >5000 mg/kg	IV	M: LD_{50} >2000 mg/kg F: LD_{50} >2000 mg/kg	III
Acute Inhalation - Rats (Dust)	M: LC_{50} >5.057 mg/L F: LC_{50} >5.057 mg/L	IV	Waived (Based on Technical data)	IV
Primary Eye Irritation - Rabbits	Not an eye irritant	IV	Not an eye irritant	IV
Primary Skin Irritation - Rabbits	Not a dermal irritant	IV	Slight dermal irritation	IV
Dermal Sensitization - Guinea Pigs	Not a dermal sensitizer	N/A	Not a dermal sensitizer	N/A

Subchronic & Chronic Toxicity

STUDY TYPE	RESULTS
Acute Neurotoxicity - Rat	Male NOAEL = 630 mg/kg/day LOAEL = 2000 mg/kg/day (Highest Dose Tested (HDT)) Female NOAEL = 2000 mg/kg/day (HDT) LOAEL = Not established
28-Day Oral (Gavage) - Rat (Range-Finding)	Male NOAEL = 1000 mg/kg/day (HDT) LOAEL = Not established Female NOAEL = 1000 mg/kg/day (HDT) LOAEL = Not established
13-Week Feeding - Rat	Male NOAEL = 415 mg/kg/day LOAEL = 904 mg/kg/day Female NOAEL = 1132 mg/kg/day LOAEL = 2824 mg/kg/day
13-Week Feeding - Dog	Male NOAEL = 34 mg/kg/day LOAEL = 239 mg/kg/day Female NOAEL = 37 mg/kg/day LOAEL = 261 mg/kg/day
14-Week Feeding - Mouse (Range-Finding)	Male NOAEL = 267 mg/kg/day LOAEL = 3284 mg/kg/day Female NOAEL = 454 mg/kg/day LOAEL = 5151 mg/kg/day
21-Day Dermal Toxicity - Rabbit	Male NOAEL (systemic) = 1000 mg/kg/day (HDT) LOAEL (systemic) = Not established NOAEL (dermal) = 1000 mg/kg/day (HDT) LOAEL (dermal) = Not established Female NOAEL (systemic) = 1000 mg/kg/day (HDT) LOAEL (systemic) = Not established NOAEL (dermal) = 1000 mg/kg/day (HDT) LOAEL (dermal) = Not established
5-Day Inhalation - Rat DUST (Range-Finding)	Male NOAEL = 0.098 mg/L LOAEL = 1.093 mg/L Female NOAEL = 0.098 mg/L LOAEL = 1.093 mg/L
1-Year Chronic Feeding - Dog	Male NOAEL = 17 mg/kg/day LOAEL = 124 mg/kg/day Female NOAEL = 19 mg/kg/day LOAEL = 133 mg/kg/day
2-Year Chronic Toxicity/ Carcinogenicity - Rat	Male NOAEL = 28 mg/kg/day LOAEL = 292 mg/kg/day Female NOAEL = 40 mg/kg/day LOAEL = 415 mg/kg/day

Developmental & Reproductive Toxicity

STUDY TYPE	RESULTS
Developmental Toxicity - Rat	Maternal NOAEL < 1044 mg/kg/day LOAEL = 1044 mg/kg/day Developmental NOAEL = 1044 mg/kg/day (HDT) LOAEL = Not established
Developmental Toxicity - Rabbit	Maternal NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day Developmental NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day
2-Generation Reproductive Toxicity - Rat	Parental Males NOAEL = 38 mg/kg/day LOAEL = 406 mg/kg/day Females NOAEL = 45 mg/kg/day LOAEL = 477 mg/kg/day Offspring Males NOAEL = 38 mg/kg/day LOAEL = 406 mg/kg/day Females NOAEL = 45 mg/kg/day LOAEL = 477 mg/kg/day

Mutagenicity & Carcinogenicity

STUDY TYPE	RESULTS
2-Year Chronic Toxicity/ Carcinogenicity - Rat	No evidence of carcinogenicity
2-Year Carcinogenicity - Mouse	Male NOAEL = 247 mg/kg/day LOAEL = 807 mg/kg/day Female NOAEL = 1055 mg/kg/day LOAEL = 3178 mg/kg/day No evidence of carcinogenicity
Reverse Gene Mutation - *Salmonella*	Non-mutagenic (±) activation
Forward Gene Mutation - HGPRT locus	Non-mutagenic (±) activation
Micronucleus Assay - Mice	Non-mutagenic
Unscheduled DNA Synthesis -Rat Hepatocytes	Non-mutagenic
Chromosome Aberration - CHO cells	Non-mutagenic (±) activation

Metabolism & Dermal Absorption

STUDY TYPE	RESULTS
Metabolism - Rat	Rapidly & completely absorbed/excreted (<48 hours); Pronounced enterohepatic circulation. Metabolite in bile - glucuronide; Major route of excretion/feces (mostly parent); Lesser amounts in urine (mostly glucuronide).
Dermal Absorption - Rat	At 10 hours, mean dermal absorption was 20% (low dose group)

FOOD QUALITY PROTECTION ACT (FQPA) SAFETY FACTOR

- EPA determined that a **FQPA 3X** safety factor is required to assess chronic dietary risk since, *qualitatively*, there is evidence of increased susceptibility in rat pups compared to adults, based on the relative severity of effects in the two-generation reproduction study in rats. The 3X applies to all population subgroups.

TOXICOLOGICAL ENDPOINTS

- **Acute: An acute Reference Dose (RfD)** was not identified because there were no adverse effects attributable to a single (acute) exposure.

- **Chronic: A chronic RfD of 0.17 mg/kg/day** was selected (NOAEL = 17 mg/kg/day) for use in assessing chronic dietary risk. This RfD is based on the 1-year chronic oral toxicity study in dogs, in which decreased red blood cell (RBC) counts, hemoglobin and hematocrit and increased Heinz bodies in RBC were seen at the LOAEL of 124/133 mg/kg/day in males/females; also, in females, increased absolute and relative adrenal weights correlated with histopathological observations of increases in the incidence and severity of intracytoplasmic vacuoles in the adrenal cortex.

  The chronic population-adjusted dose (cPAD) = 0.057 mg/kg/day when the chronic RfD (0.17 mg/kg/day) is divided by FQPA 3X safety factor.

- **Short- and Intermediate-Term:** The NOAEL of 1000 mg/kg/day from the 21-day dermal toxicity study in rabbits was selected for dermal exposure. The endpoint was decreased body weight gain and food consumption noted at the LOAEL of 1500 mg/kg/day (20% dermal absorption factor). This dermal endpoint applies only to occupational exposure as there are no residential uses of fenhexamid.

- **Cancer Classification:** Fenhexamid is classified as a "not likely" human carcinogen according to the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (4/10/96). The classification is based on the lack of evidence of carcinogenicity in male and female rats, as well as in male and female mice, and on the lack of genotoxicity in an acceptable battery of mutagenicity studies. A risk assessment was not required.

DIETARY EXPOSURE

EPA used the Dietary Exposure Evaluation Model (DEEM) to conduct a chronic dietary (food) risk analysis. DEEM is a dietary exposure analysis system that is used to estimate exposure to a pesticide chemical in foods comprising the diets of the U.S. population, including various population subgroups. DEEM contains food consumption data as reported by respondents in the USDA Continuing Surveys of Food Intake by Individuals conducted in 1989-1992. The chronic dietary exposure analysis is as follows:

Chronic Dietary Exposure Analysis Using DEEM			
Population Subgroups [1]	**Exposure (mg/kg/day)**	**% of Chronic RfD [2]**	**% of cPAD [3]**
U.S. Population (48 states - all seasons)	0.000982	0.6	1.8
All infants (<1 year)	0.002021	1.2	3.6
Nursing infants (<1 year)	0.003723	2.2	**6.6**
Non-nursing infants (<1 year)	0.001305	0.8	2.4
Children (1-6 years)	0.002805	1.6	4.8
Children (7-12 years)	0.001069	0.6	1.8
U.S. Population - summer season	0.001119	0.7	2.1
Western region	0.001347	0.8	2.4
Pacific region	0.001515	0.9	2.7
Non-hispanic other than black or white	0.001442	0.8	2.4
Females (13+/nursing)	0.002091	1.2	3.6

1 The subgroups listed are:
(1) the U. S Population (48 states - all seasons);
(2) those for infants and children;
(3) Other subgroup(s) for which the percentage of the Chronic RfD occupied is greater than that occupied by the subgroup U. S Population (48 states - all seasons); and,
(4) the most highly exposed of the females subgroups (in this case, Females, 13+/nursing)

2 Percent Chronic RfD = (Exposure ÷ Chronic RfD) x 100%.

3 Percent cPAD = (Exposure ÷ cPAD) x 100%.

DRINKING WATER EXPOSURE

The Agency is presently relying on computer-generated estimated environmental concentrations (EECs) from the Generic Estimated Environmental Concentration (GENEEC) and the Screening Concentration in Ground Water (SCI-GROW) models. These models take into account the use patterns and the environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for assessing whether a pesticide is likely to be present in drinking water at concentrations which would exceed human health levels of concern. The SCI-GROW model generates a single EEC value of pesticide concentration in *ground* water which is used in assessments of both acute and chronic dietary risk. The GENEEC model generates several time-based EEC values of pesticide concentration in *surface* water, ranging from 0-days (peak) to 56-days (average). The GENEEC peak EEC is used in assessments of acute dietary risk, and the GENEEC 56-day (average) EEC is used in assessments of chronic (non-cancer and cancer) dietary risk.

EPA calculates a drinking water level of comparison (DWLOC) which is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses (N/A - no residential uses for

fenhexamid). DWLOCs are used in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs. When DWLOCs are less than EECs, EPA considers the aggregate risk [from food + water + (if applicable) residential exposures] to be acceptable. DWLOCs for specific population subgroups and EECs estimated for fenhexamid are as follows:

DWLOCs and EECs			
Population Subgroup	**DWLOC (μg/L) [2,3,4]**	**SCI-GROW (μg/L)**	**GENEEC 56-day avg (μg/L)**
U.S. Population (48 states, all seasons)	2000	0.0007	4.8
Females 13+ *	1700		
Infants/Children*	**530**		
Other *	1900		

*Within each of these subgroups, the subpopulation with the highest (chronic) food exposure was selected; namely, Females (13+/nursing); Nursing infants (<1 year); and, the Pacific region, respectively.

AGGREGATE EXPOSURE

Chronic (non-cancer) aggregate risk is the sum of exposure resulting from chronic dietary food + chronic drinking water + chronic residential uses. Fenhexamid has no registered residential uses. Therefore, this risk assessment is the aggregate of chronic dietary food + chronic drinking water exposures only. The SCI-GROW and GENEEC chronic EEC values are less than the Agency's level of concern (the DWLOC value for each population subgroup) for fenhexamid residues in drinking water as a contribution to chronic aggregate exposure. Therefore, EPA concludes with reasonable certainty that residues of fenhexamid in drinking water will not contribute significantly to the aggregate chronic human health risk and that the chronic aggregate exposure from fenhexamid residues in food and drinking water will not exceed EPA's level of concern (100% of the chronic PAD or cPAD) for chronic dietary aggregate exposure by any population subgroup. EPA generally has no concern for exposures below 100% of the cPAD, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of any population subgroup.

OCCUPATIONAL EXPOSURE

Workers may be exposed to fenhexamid during mixing, loading, application and post-application activities. Based on the application rates and use scenarios, short- and intermediate-term exposures may occur. EPA used surrogate data from the Pesticide Handlers Exposure Data base (PHED) to assess handler exposures. PHED is a software system consisting of two parts (a data base of measured exposure values for workers involved in handling pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize selected data). All Margins of Exposure (MOEs) are above 100 and do not exceed EPA's level of concern. A summary is provided below:

OCCUPATIONAL HANDLER DERMAL EXPOSURES TO FENHEXAMID			
PHED Exposure Scenario	Application Rates (lb ai/acre or lb ai/gal)	Crop	MOEs
Mixer/ Loader Exposure			
Mixing/Loading Dry flowable Formulation (WDG) for Groundboom	0.50	Grapes	23,000
	0.75	Strawberries and Ornamentals	15,000
Mixing/Loading Dry flowable Formulation (WDG) for Airblast Spray	0.50	Grapes	45,000
	0.75	Strawberries and Ornamentals	30,000
Applicator Exposure			
Applying Sprays with Groundboom	0.50	Grapes	110,000
	0.75	Strawberries and Ornamentals	71,000
Applying Sprays with Airblast	0.50	Grapes	12,000
	0.75	Ornamentals	8,300
Mixer/Loader/Applicator Exposure			
Mixing/loading/Applying Spray with High Pressure Handwand	0.005	Grapes	17,000
	0.0075	Strawberries and Ornamentals	11,000
Mixing/loading/Applying Spray with Low Pressure Handwand	0.0075	Ornamentals	450,000

WORKER POSTAPPLICATION ACTIVITIES		
Crop	**Worker Activity**	**MOE**
Grapes	harvest, hand girdle, cane, tie, prune, thin, tip	450
Strawberries	hand harvest, scout, irrigate	1000
Indoor/outdoor ornamental	indoor (cut/harvest, prune); outdoor (transplant, ball/burlap)	450

ECOLOGICAL EFFECTS CHARACTERISTICS

Based on the proposed multiple (4) applications at a maximum rate of 0.75 lbs. a.i./acre, the acute toxicity data for Fenhexamid can be summarized as follows:

- Avian acute oral - practically nontoxic (LD_{50} > 2,000 mg/kg)
- Avian acute - practically nontoxic (LC_{50} > 5,000 ppm)
- Avian chronic - potential chronic effect due to fenhexamid-induced anorexia (NOAEC 2,074 ppm)
- Mammalian acute - practically nontoxic (LC_{50} >5,000 ppm)
- Mammalian chronic - potential chronic reproductive effect with decreased neonatal body weight (NOAEL 500 ppm)
- Honey bee acute - practically nontoxic to adult bees (LD_{50} > μg/bee)
- Fish (freshwater) acute - moderately toxic (LC_{50} 1.34 - 3.42 ppm)
- Fish (marine/estuarine) acute - moderately toxic (LC_{50} 11 ppm)
- Invertebrates (freshwater) acute - slightly toxic (EC_{50} > 18.8 ppm)
- Invertebrates (freshwater) chronic - (NOAEC 1.0 ppm)
- Invertebrates (marine/estuarine) acute - moderately toxic (EC_{50} 4.6 ppm)
- Aquatic plant acute (EC_{50} 1.37 ppm)

ENVIRONMENTAL FATE CHARACTERISTICS

Fenhexamid is not persistent in the environment under aerobic conditions and is unlikely to reach surface or ground water; however, if fenhexamid reached an anaerobic environment, it would be considered moderately persistent.

- Fenhexamid is stable to hydrolysis but rapidly degrades in laboratory aqueous photolysis studies. The major photolytic degradation products were dechlorinated and hydroxylated forms of fenhexamid and CO_2.

- Fenhexamid is considered non-persistent in aerobic terrestrial systems (DT50 < 1 day), undergoing rapid polymerization, irreversible binding, and eventual mineralization in the soil matrix. Carbon dioxide and unidentified unextractable residues accounted for approximately 30 and 60% of applied, respectively, at the conclusion of the aerobic soil metabolism study. However, the submitted data indicates the rapid dissipation of fenhexamid may be the result of polymerization in soil due to the organic solvent carrier.

- In laboratory aerobic aquatic systems (DT50 14-24 days) over 70% of the applied ^{14}C had partitioned to the sediment and was unidentified by 100 days where up to ~6% of total residues were identified as fenhexamid.

- Fenhexamid is considered immobile under typical use conditions based on field dissipation studies where the fungicide did not leach (K_d ~ 3-11). Also, batch equilibrium studies indicate fenhexamid will have low mobility in most soils. Thus, transport of fenhexamid in the environment will most likely occur in association with movement of soil particles.

SUMMARY OF DATA GAPS

- A field dissipation study (Guideline No. 164-1)
- An aerobic soil metabolism study (Guideline No. 162-1)
- A fish bioaccumulation study (Guideline No. 165-4)

TOLERANCES ESTABLISHED FOR RESIDUES OF FENHEXAMID

- Grapes..... 4.0 ppm
- Raisins ..... 6.0 ppm
- Strawberries..... 3.0 ppm

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