United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

Pesticide Fact Sheet

Name of Chemical: **Cyazofamid**
Reason for Issuance: **New Chemical**
Date Issued: **September 2004**

DESCRIPTION OF CHEMICAL

Chemical Name:	4-chloro-2-cyano-*N,N*-dimethyl-5-(4-methylphenyl)-1*H*-imidazole-1-sulfonamide
Common Name:	Cyazofamid
Trade Name:	Ranman™ 400SC
Chemical Class:	Cyanoimidazole
EPA Chemical Code:	085651
Chemical Abstracts Service (CAS) Number:	120116-88-3
Year of Initial Registration:	2004
Pesticide Type:	Fungicide
U.S. Producer:	ISK Biosciences Corporation Concord, OH

USE PATTERN AND FORMULATIONS

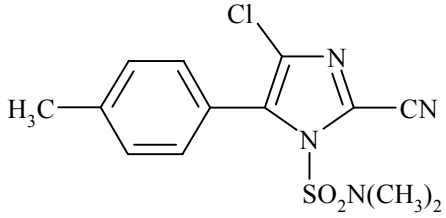
ISK Biosciences Corporation has registered a manufacturing use and an end-use product containing cyazofamid. The end-use product, Ranman 400SC is a suspension concentrate with 34.5% active ingredient (a.i.) used for control of diseases caused by oomycete fungi. The product controls early and late blight on tomatoes and potatoes and downy mildew on cucurbit vegetables (crop group 9). An import tolerance for imported grape wine has been established. Cyazofamid has limited systemic activity so it is used as a protectant fungicide applied by ground or aerial spray. The biochemical mode of action of cyazofamid is inhibition of all stages of fungal development.

SUMMARY OF SCIENCE FINDINGS

PHYSICAL/CHEMICAL PROPERTIES

Table 1. Chemical Identity, Structure and Properties of Cyazofamid Technical

Common Name	Cyazofamid	
IUPAC name	4-chloro-2-cyano-*N,N*-dimethyl-5-*p*-tolylimidazole-1-sulfonamide	
CAS name	4-chloro-2-cyano-*N,N*-dimethyl-5-(4-methylphenyl)-1*H*-imidazole-1-sulfonamide	
CAS #	120116-88-3	
PC Code	085601	
Empirical Formula	$C_{13}H_{13}ClN_4O_2S$	
Molecular Weight	324.9	
Melting point	152.7° C	
pH	4.9 at 25° C	
Relative Density (D_4^{20})	1.446	
Water solubility (@ 20° C $\pm$ 1°C)	0.107 mg/L at pH 7	
Solvent solubility (equilibrated @ 21.2 $\pm$ 1° C)	Organic solvents	(g/100 mL)
	hexane methanol acetonitrile dichloroethane toluene ethyl acetate acetone octanol	0.003 0.174 3.095 10.212 0.600 1.649 4.564 0.004
Vapor pressure	$<1.33 \times 10^{-5}$ Pa (@ 25, 30, 35°C)	
Dissociation constant, pKa	no pK_a evident in pH range 2-12	
Octanol/water partition coefficient, K_{ow}	3.2	
Half-Lives	Aerobic soil: 5.5 days Aerobic Aquatic: 16.4 days Aquatic Photolysis: 0.02 days	

Table 1. Chemical Identity, Structure and Properties of Cyazofamid Technical	
Cyazofamid - chemical structure	

TOXICOLOGICAL CHARACTERISTICS:

Acute Toxicity: Technical grade cyazofamid has minimal to moderate acute toxicity in acute oral, dermal and inhalation tests, it is minimally irritating to the eyes and skin, and is a weak dermal sensitizer.

Table 2. Acute Toxicity of Cyazofamid - Technical.

Guideline No.	Study Type	Results	Toxicity Category
870.1100	Acute Oral – Rat	LD_{50}> 5000 mg/kg [M/F]	IV
870.1200	Acute Dermal – Rat	LD_{50} > 2000 mg/kg [M/F]	III
870.1300	Acute Inhalation – Rat	LC_{50} > 5.5mg/L [M/F]	IV
70.2400	Primary Eye Irritation – Rabbit	Grade 2 conjunctival redness and discharge that resolved by 24 hours	IV
870.2500	Primary Skin Irritation – Rabbit	Very slight to well defined erythema that cleared by 7 days	III
870.2600	Dermal Sensitization (Guinea Pig Maximization test)	Positive (weak sensitizer)	-

Subchronic Toxicity: Following repeated administration in more than one species, cyazofamid seems to have mild or low toxicity. The kidney seemed to be a target organ following 13 weeks of dietary feeding in male rats of the high dose group (5,000 ppm or 295 mg/kg/day) which had increased microscopic kidney lesions characterized as "increased number of basophilic tubules, graded as slight" in addition to mild increases in urinary output, protein, and pH. Female rats of the same study were less sensitive; with the only change being a marginal increase in urine volume and pH seen only at the highest dose of 20,000 ppm (1395 mg/kg/day).

Chronic Toxicity: Skin lesions, which may be due to systemic allergy, were observed in the males of the 18 month carcinogenicity study. At the high dose, approaching 1,000 mg/kg/day, male mice suffered hair loss due to scratching which was confirmed at necropsy by increased

incidence of body sores (head, neck, trunk, limb, and/or tail), and was correlated histologically with increased incidence of acanthosis (hyperplasia), chronic active dermatitis, ulceration, and premature death. The sulfonamide moiety in the cyanoimidazole ring might have rendered cyazofamid allergenic, albeit a weak one at that. This is supported by the fact that, cyazofamid is a moderate irritant (III) in the primary rabbit skin test and is a positive weak sensitizer in the guinea pig skin maximization test. Of note, however, is that there were no skin allergies in the rat feeding study; this is not surprising, however, due to possible species variation. Sulfonamide antimicrobial drugs (e.g., sulfamethoxazole) have been know to cause idiosyncratic drug reactions in some patients with skin reactions (delayed type) ranging from benign rash to potentially lethal toxidermias.

Cyazofamid's overall toxicity profile in dogs seems to be limited. In both the 13 week and one year dog studies, there were no major toxicity findings up to a dose of 1,000 mg/kg/day. The only possible effect was increased cysts in parathyroids of both sexes and pituitary in females observed in the high dose groups of the one year study. These findings might be incidental to treatment, but because the corresponding historical control data were requested, but not provided, there is no way to know if these are common incidences in this strain. Nonetheless, the findings are considered adverse until the Registrant demonstrates that the incidences are within the range of historical control findings.

Carcinogenicity: There is no evidence that cyazofamid may be carcinogenic, as indicated in both the rat and the mouse carcinogenicity studies. It is classified as "not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in both the rat and the mouse.

Developmental and Reproductive Toxicity: The pre- and post-natal toxicology database for cyazofamid includes rat and rabbit developmental toxicity studies and two-generation reproduction toxicity study in rats. There was some evidence of increased susceptibility following *in utero* exposure to rats in the prenatal developmental toxicity study; the increased incidence of bent ribs in the high dose fetuses was considered adverse and was used for setting the developmental NOAEL/LOAEL. The Agency considered this approach conservative because bent ribs are a reversible developmental anomaly rather than a malformation.

In the prenatal developmental toxicity study in rabbits, there were no maternal or developmental effects at any dose up to the limit dose of 1,000 mg/kg/day. In the two-generation reproduction study, the highest dose tested (>1,000 mg/kg/day) did not cause maternal systemic toxicity nor did it elicit reproductive or offspring toxicity.

Neurotoxicity: In the acute neurotoxicity study, there were no indications of treatment-related adverse neurotoxicity findings including clinical signs, qualitative or quantitative neurobehavioral effects, brain weight, or gross/microscopic pathology. The Agency concluded that the slight increase in motor activity at day 14 among the mid- and high-dose males is

marginal and should not be considered an adverse finding.

Mutagenicity: Cyazofamid does not appear to have mutagenicity potential, based on several negative *in vivo* and *in vitro* studies.

Metabolism: Pharmacokinetics and metabolism studies in rats following administration of a single low (0.5 mg/kg) or high (1,000 mg/kg) dose, showed relatively rapid absorption (irrespective of dose t_{cmax} = 0.25-0.5 hrs) and elimination ($t_{1/2}$ 4.4-5.8 hrs) at the low dose and saturated absorption with prolonged elimination ($t_{1/2}$ of 7.6-11.6 hrs) at the high-dose. The extent of absorption (expressed as percent of administered dose) was highly dose-dependent, being nearly 75% at the low dose and only about 5% at the high dose. Both the urine and feces were major routes of excretion at the low dose with most of the urinary radioactivity being a metabolite named CCBA (4-(4-chloro-2-cyanoimidazol-5-yl)benzoic acid). Results of biliary excretion experiments showed biliary elimination of radiolabel to be highly variable at the low dose (~12-39% of the administered low dose) and negligible (<2%) in the high-dose groups. Urinary or biliary excretion in rats of the high-dose groups was low (each ~2%) with most of the radioactivity being CCBA. Irrespective of the dosing regimen, most of the recovered fecal radioactivity was unchanged parent compound; the major fecal metabolites were CCBA and 4-chloro-5-*p*-tolylimidazole-2-carbonitrile (CCIM) each of which being less than 5% of the administered dose. Tissue burdens at $t_{1/2}$, t_{max}, and at 168 hours post dose were indicative of rapid clearance and low tissue burdens suggesting little or no bioaccumulation or sequestration.

Metabolite Toxicity: Acute oral toxicity studies were submitted for cyazofamid metabolites CCIM, and CCIM-AM. CCIM is a major metabolite in some plant commodities (wine), while CCIM-AM is a minor metabolite. CCIM appears to be more acutely toxic (Toxicity Category III) than cyazofamid (Toxicity Category IV). However, CCIM is not a terminal metabolite and continues to degrade in plants, livestock and the environment. Metabolism and pharmacokinetics studies indicate that cyazofamid uptake is saturable with 75% being absorbed following a single dose of 0.5 mg/kg and 5% at the much higher dose of 1000 mg/kg. *In vitro* uptake studies indicate that CCIM is absorbed more readily than cyazofamid. Thus, the difference in acute oral toxicity probably reflects poor uptake of cyazofamid at high doses and is not likely to be relevant to the lower doses expected from dietary exposure where cyazofamid is absorbed readily.

Table 3. Toxicity Profile of Cyazofamid Technical.

Guideline No.	Study Type	Results
870.3100	90-Day oral toxicity in rats	NOAEL = 29.5 [M] mg/kg/day LOAEL = 295 [M] mg/kg/day based on increased number of "basophilic kidney tubules," and increased urinary volume, pH, and protein.

Table 3. Toxicity Profile of Cyazofamid Technical.		
Guideline No.	**Study Type**	**Results**
870.3150	90-Day oral toxicity in dogs	NOAEL = 1,000 [M/F] mg/kg/day LOAEL = not observed.
870.3200	28-Day dermal toxicity in rats	NOAEL = 1,000 [M/F] mg/kg/day LOAEL = not observed.
870.3700a	Prenatal developmental in rats	**Maternal** NOAEL = 1,000 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 100 mg/kg/day LOAEL = 1,000 mg/kg/day based on increased incidence of bent ribs.
870.3700b	Prenatal developmental in rabbits	**Maternal** NOAEL = 1,000 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 1,000 mg/kg/day LOAEL = not observed
870.3800	Reproduction and fertility effects in rats	**Parental/Systemic** NOAEL = 1114/ 1416 [M/F] mg/kg/day LOAEL = not observed **Reproductive** NOAEL = 1114/ 1416 [M/F] mg/kg/day LOAEL = not observed **Offspring** NOAEL = 1114/ 1416 [M/F] mg/kg/day LOAEL = not observed
870.4100a	Chronic toxicity in rats	NOAEL = 171/ 856 [M/F] mg/kg/day LOAEL = not observed.
870.4100b	Chronic toxicity in dogs	NOAEL = 200 [M/F] mg/kg/day LOAEL = 1,000 [M/F] mg/kg/day based on increased cysts in parathyroids in both sexes and increased pituitary cysts in females.
870.4200	Carcinogenicity rats	NOAEL = 171/ 856 [M/F] mg/kg/day LOAEL = not observed. **No evidence of carcinogenicity**
870.4300	Carcinogenicity mice	NOAEL = 94.8 [M] mg/kg/day LOAEL = 985 [M] mg/kg/day based on increased incidence of skin lesions including hair loss, body sores, dermatitis, ulceration, and acanthosis. **No evidence of carcinogenicity**
870.5100	Gene Mutation Bacterial reverse mutation assay	**Negative** ± S9 up to 5,000 μg/plate by standard plate and tube preincubation (not cytotoxic but there was precipitation at ≥1,500 µg/plate.

Table 3. Toxicity Profile of Cyazofamid Technical.		
Guideline No.	**Study Type**	**Results**
870.5300	Gene Mutation Mammalian cell culture	**Negative** ± S9 up to cytotoxic and precipitating concentration of 100 μg/mL
870.5375	Cytogenetics Chromosomal aberrations	**Negative** ± S9 for clastogenic/aneugenic activity up to cytotoxic and precipitating 200 μg/mL
870.5395	Cytogenetics Micronucleus test on mouse	**Negative** up to the highest dose tested (limit dose) 2,000 mg/kg
870.5500	Other Effects Bacterial DNA repair test (Rec-assay)	**Negative** ± S9 up to limit of solubility at 8,000 μg/disc
870.7485	Metabolism and pharmacokinetics in rats	There was rapid absorption (irrespective of dose t_{cmax} = 0.25-0.5 hrs) and rapid elimination at the low dose ($t_{1/2}$ 4.4-5.8 hrs) while there was saturated absorption with prolonged elimination ($t_{1/2}$ of 7.6-11.6 hrs) at the high-dose. The extent of absorption (as percent of administered dose) was highly dose-dependent being nearly 75% at the low dose and only about 5% at the high dose. Both the urine and feces were major routes of excretion at the low dose with most of the urinary radioactivity being a metabolite named CCBA (4-(4-chloro-2-cyanoimidazol-5-yl)benzoic acid). The biliary elimination was highly variable at the low dose (~12-39% of the administered low dose) and negligible (<2%) in the high-dose groups. Urinary or biliary excretion in the high-dose groups was low (each ~2%) with most of the radioactivity being CCBA. Irrespective of the dosing regimen, most of the recovered fecal radioactivity was unchanged parent compound; the major fecal metabolites were CCBA and 4-chloro-5-*p*-tolylimidazole-2-carbonitrile (CCIM) each of which being less than 5% of the administered dose. Tissue burdens at $t_{1/2}$, t_{max}, and at 168 hours post dose indicated rapid clearance and low tissue burdens suggesting little or no bioaccumulation or sequestration.

FOOD QUALITY PROTECTION ACT (FQPA) SAFETY FACTOR

The Agency evaluated the potential for increased susceptibility of infants and children from exposure to cyazofamid according to the February 2002 Agency 10X guidance document. Since there are no concerns or residual uncertainties for pre- and or postnatal toxicity, the Agency concluded that the special FQPA safety factor (SF) should be removed [i.e., reduced to 1X] for all potential exposure scenarios to cyazofamid. Additionally, the cyazofamid risk assessment team evaluated the quality of the exposure data, and based on these data, agreed that the special FQPA Safety Factor could be reduced to 1X. The recommendation is based on the following:

- In the rat developmental toxicity study, there was quantitative evidence of *in utero* susceptibility; increases in fetuses with bent ribs were seen at 1,000 mg/kg/day (top dose) in the absence of maternal toxicity. The developmental NOAEL was 100 mg/kg/day and the maternal NOAEL was 1,000 mg/kg/day. The Agency concluded that bent ribs are a reversible developmental anomaly rather than a malformation and that using this endpoint for setting the developmental NOAEL/LOAEL is a conservative approach.
- In the prenatal developmental toxicity study in rabbits, there was no indication of increased susceptibility (qualitative or quantitative) of rabbit fetuses to *in utero* exposure to cyazofamid. No maternal or developmental effects were seen at any dose up to the limit dose of 1,000 mg/kg/day.
- In the two-generation reproduction study, the highest dose tested (>1,000 mg/kg/day) did not cause maternal systemic toxicity nor did it elicit reproductive or offspring toxicity.
- The Agency concluded that the concern is low for the quantitative susceptibility seen in the rat developmental toxicity study and there are no residual uncertainties because:
    1. The developmental effect is well identified with clear NOAEL/LOAEL;
    2. The developmental effect (increased bent ribs) is a variation rather than a malformation;
    3. The developmental effect is seen only at the limit dose of 1,000 mg/kg/day;
    4. This endpoint is used to establish the acute RfD for Females 13-49;
    5. The overall toxicity profile indicates that cyazofamid is not a very toxic compound.
- There were no indications of pre- or postnatal toxicity and no residual uncertainties from the rabbit developmental study or the rat two generation reproduction study.
- The exposure assessments are Tier 1, conservative, high-end assessments and will not underestimate the potential dietary (food and water) exposures.
- There are no proposed residential uses.

TOXICOLOGICAL ENDPOINTS

Table 4. Summary of Toxicological Doses and Endpoints for Cyazofamid			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-50 years of age)	NOAEL = 100 mg/kg UF = 100 **Acute RfD** = 1.0 mg/kg	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = **1.0** mg/kg	Rat Prenatal Developmental Toxicity (MRID 45408933) LOAEL = 1,000 mg/kg based on developmental toxicity findings of increased incidence of bent ribs.
Acute Dietary (General population including infants and children)	NOAEL = NA UF = NA **Acute RfD** = NA	FQPA SF = NA aPAD = acute RfD / FQPA SF = NA	Not Required. No adverse effects were observed which could be attributed to a single-dose exposure.
Chronic Dietary (All populations)	NOAEL= 94.8 mg/kg/day UF = 100 **Chronic RfD** = 0.95 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.95 mg/kg/day	18-Month Mouse Oral Carcinogenicity (MRID 45408932) LOAEL = 985 mg/kg/day based on increased skin lesions.
Short- (1-30 days) and Intermediate-Term (1 to 6 months) Incidental Oral	NOAEL= NA No Residential Uses	**Residential** LOC for MOE = NA **Occupational** = NA	
Short- (1-30 days) and Intermediate-Term (1 to 6 months) Dermal	Oral study NOAEL = 100 mg/kg/day (dermal absorption rate = 37 %)	**Residential** LOC for MOE = NA **Occupational** LOC for MOE = 100	Rat Prenatal Developmental Toxicity (MRID 45408933) LOAEL = 1,000 mg/kg based on developmental toxicity findings of increased incidence of bent ribs.
Long-Term Dermal (>6 months)	Oral study NOAEL = 94.8 mg/kg/day (dermal absorption rate = 37 %)	**Residential** LOC for MOE = NA **Occupational** LOC for MOE = 100	18-Month Mouse Oral Carcinogenicity (MRID 45408932) LOAEL = 985 mg/kg/day based on increased skin lesions.
Short- (1-30 days) and Intermediate-Term (1 to 6 months) Inhalation	Oral study NOAEL = 100 mg/kg/day	**Residential** LOC for MOE = NA **Occupational** LOC for MOE = 100	Rat Prenatal Developmental Toxicity (MRID 45408933) LOAEL = 1,000 mg/kg based on developmental toxicity findings of increased incidence of bent ribs.
Long-Term Inhalation (>6 months)	Oral study NOAEL = 94.8 mg/kg/day	**Residential** LOC for MOE = NA **Occupational** LOC for MOE = 100	18-Month Mouse Oral Carcinogenicity (MRID 45408932) LOAEL = 985 mg/kg/day based on increased skin lesions.

Table 4. Summary of Toxicological Doses and Endpoints for Cyazofamid			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (oral, dermal, inhalation)	Not Applicable	NA	NA

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, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

DIETARY EXPOSURE

ACUTE DIETARY

A Tier 1 (unrefined) acute dietary exposure analysis was conducted using DEEM-FCID™ and Lifeline™ for cyazofamid. As an acute dietary endpoint was not identified for the general population including infants and children, the acute dietary analysis was performed for the population subgroup Females 13 to 49 years old only. The assumptions of this dietary exposure assessment are tolerance level residues and 100% crop-treated.

At the 95th percentile of exposure, the Tier 1 acute DEEM-FCID™ and Lifeline™ analysis gave the results listed in Table 5. For the acute analysis, the exposure at the 95th percentile for Females 13 to 49 years old is 0.003769 mg/kg/day for DEEM-FCID™ or 0.004013 mg/kg/day for Lifeline™, which utilizes <1% of the acute PAD for cyazofamid for both DEEM-FCID™ and Lifeline™. The results of the Lifeline™ analysis are fully consistent with the DEEM-FCID™ results.

Table 5. Acute Dietary Exposure Estimates for Cyazofamid					
Population Subgroup	**aPAD (mg/kg/day)**	**DEEM-FCID™**		**LifeLine™**	
		Exposure (mg/kg/day)	**%aPAD[1]**	**Exposure (mg/kg/day)**	**%aPAD[1]**
Females 13-49 years old	1.0	0.003769	<1	0.004013	<1

[1] Percent Acute PAD = (Exposure ÷ Acute PAD) x 100%.

CHRONIC DIETARY

An unrefined chronic dietary exposure analysis (Tier 1 assessment) was conducted via DEEM-FCID™ and LifeLine™ for cyazofamid. The assumptions of this dietary exposure assessment

are tolerance level residues and 100% crop-treated.

The Tier 1 chronic DEEM-FCID™ and Lifeline™ analysis gave the results listed in Table 6. For the chronic analysis, the most highly exposed population subgroup and the highest risk estimate was for Children 1 to 2 years old. The chronic exposures for Children 1 to 2 years old are 0.004778 mg/kg/day for DEEM-FCID™ or 0.004529 mg/kg/day for Lifeline™, which utilize <1.0% (for both DEEM-FCID™ and Lifeline™) of the chronic PAD for cyazofamid. The results of the Lifeline™ analysis are fully consistent with the DEEM-FCID™ results.

Table 6. Chronic Dietary Exposure Estimates for Cyazofamid.

Population Subgroup	cPAD (mg/kg/day)	DEEM-FCID™		LifeLine™	
		Exposure (mg/kg/day)	%cPAD[1]	Exposure (mg/kg/day)	% cPAD[1]
General U.S. Population	0.95	0.001016	<1	0.000988	<1
All Infants (< 1 year old)	0.95	0.001448	<1	0.001501	<1
Children 1-2 years old	**0.95**	**0.004778**	**<1**	**0.004529**	**<1**
Children 3-5 years old	0.95	0.003101	<1	0.003236	<1
Children 6-12 years old	0.95	0.001338	<1	0.00131	<1
Youth 13-19 years old	0.95	0.000567	<1	0.000589	<1
Adults 20-49 years old	0.95	0.000684	<1	0.000751	<1
Adults 50+ years old	0.95	0.000774	<1	0.000802	<1
Females 13-49 years old	0.95	0.000720	<1	0.000816	<1

[1] Percent Chronic PAD = (Exposure ÷ Chronic PAD) x 100%.

ESTIMATED DRINKING WATER CONCENTRATIONS (EDWCS)

The screening level surface water and ground water estimates are calculated using Tier 1 models FIRST and SCI-GROW, respectively. The estimates are presented in Table 7.

Table 7. Estimated Concentrations of Cyazofamid in Drinking Water				
Scenario	**Residue**	**Surface Water (ppb or µg/L)**		**Ground water EDWC (ppb or µg/L)**
		Acute Value	**Chronic Value**	
1st Scenario	cyazofamid	3.103	0.047	0.002680
2nd Scenario	CCIM	2.438	1.017	0.000139
	CCIM-AM	0.805	0.419	0.000626
	CTCA	5.926	1.914	0.117000
3rd Scenario	CTCA	25.031	8.085	0.495000

Based on the results summarized in Table 7 and time-line of exposure:

- The surface water acute EDWC is 6.436 ppb (total value = Parent [3.103 ppb] + CCIM [2.438 ppb] + CCIM-AM [3.103 ppb]);
- CTCA is not expected to be present during this time frame.
- The surface water chronic EDWC is 8.085 ppb(equal to the value for the terminal degradate CTCA).
- For ground water, the value is 0.495 ppb (equal to the value for the terminal degradate CTCA).

AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Short- and intermediate-term aggregate risk is comprised of the combined exposures from food, water, dermal, inhalation and incidental oral sources (residential). These exposures are then compared to the appropriate short- or intermediate-term endpoint. Acute aggregate and chronic aggregate risk is made up of the combined dietary exposures from food and water sources.

Aggregate exposure risk assessments were performed for the following scenarios: acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Short-, intermediate-, and long-term aggregate risk assessments were not performed because cyazofamid is not registered or proposed for residential uses. A cancer aggregate risk assessment was not performed because cyazofamid has been classified as "not likely to be carcinogenic to humans".

Since the Agency does not have reliable ground and surface water monitoring data to calculate a quantitative aggregate exposure, Drinking-Water-Levels-of-Concern (DWLOCs) were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses, when applicable. A DWLOC will vary depending on the toxicity endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. The Agency uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are

not regulatory standards for the pesticide in drinking water.

To calculate DWLOCs, the dietary food estimates (from DEEM-FCID™ or Lifeline™) were subtracted from the acute or chronic PAD to obtain the maximum water exposure level. DWLOCs were then calculated using standard body weights and drinking water consumption figures as follows: 70 kg body weight/2 L water consumption (US Population; Adults 20-49; Adults 50+), 60 kg/2 L (Youth 13-19; Females 13-49), and 10 kg/1 L (All Infants and Children).

For acute and chronic dietary exposure, the Agency is concerned when estimated dietary risk exceeds 100% of the acute or chronic PAD, respectively.

ACUTE AGGREGATE RISK ASSESSMENT (FOOD AND DRINKING WATER)

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of cyazofamid (food and drinking water).

The dietary exposure analyses in this assessment for cyazofamid result in dietary risk (food only) estimates that are below the Agency's level of concern for acute dietary (food only) exposure. For the acute analysis, the exposure at the 95th percentile for Females 13 to 49 years old is 0.003769 mg/kg/day for DEEM-FCID™ or 0.004013 mg/kg/day for Lifeline™, which utilize <1% of the acute PAD for cyazofamid for both DEEM-FCID™ and Lifeline™.

The EDWCs (6.436 µg/L) are less than the calculated DWLOC for acute exposure to cyazofamid in drinking water. At the 95th percentile of exposure, for the Females 13 to 49 years old, the EDWC is less than the 30,000 µg/L or ppb DWLOC, and does not exceed the Agency's level of concern. Table 8 summarizes the acute aggregate exposure estimates to cyazofamid.

Table 8. Acute Aggregate Exposures to Cyazofamid.

Population Subgroup	aPAD (mg/kg/day)	Acute 95 % Food Exposure[1] (mg/kg/day)	Maximum Acute Water Exposure[2] (mg/kg/day)	Ground Water EDWC [3] (ppb or µg/L)	Surface Water EDWC [3] (ppb or µg/L)	Acute DWLOC [4] (ppb or µg/L)
Females 13-49 years old	1.0	0.004013	1.0	**0.495**	**6.436**	3.0×10^4

[1] The exposure from the model producing the highest exposure estimate for the population subgroup was used.
[2] Maximum Water Exposure (mg/kg/day) = aPAD (mg/kg/day) - Dietary (Food) Exposure.
[3] The highest level was used.
[4] DWLOC(µg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

A body weight of 70 kg is assumed for adults, 60 kg for females and youth, and 10 kg for children; water consumption is assumed to be 2 L for adults and 1 L for children.

As shown in Table 8 previously, the resulting dietary food exposures for Females 13 to 49 years

old occupy <1% of the acute PAD. The results of this dietary exposure analysis should be viewed as very conservative and health protective. Refinements such as use of percent crop-treated information and/or anticipated-residue values would yield even lower estimates of acute dietary exposure.

The EDWCs for assessing acute aggregate dietary risk are 0.495 µg/L (for ground water, based on SCI-GROW) and 6.436 µg/L (in surface water, based on FIRST modeling, annual average). The back-calculated DWLOC (Table 11) for assessing acute aggregate dietary risk for Females 13 to 49 years old is 30,000 µg/L.

The acute EDWCs are less than the Agency's level of comparison (the DWLOC value for Females 13 to 49 years old) for cyazofamid residues in drinking water as a contribution to acute aggregate exposure. The Agency thus concludes with reasonable certainty that residues of cyazofamid in drinking water will not contribute significantly to the aggregate acute human health risk, and that the acute aggregate exposure from cyazofamid residues in food and drinking water will not exceed the Agency's level of concern (100% of the acute PAD). EPA generally has no concern for exposures below 100% of the acute PAD. This risk assessment is considered high confidence, very conservative, and very protective of human health.

SHORT-/INTERMEDIATE-TERM AGGREGATE RISK ASSESSMENT

There are no residential uses proposed for this fungicide. Thus, short- and intermediate-term aggregate risk assessments based on exposure from oral, inhalation, and dermal routes of exposure were not performed for cyazofamid.

CHRONIC AGGREGATE RISK ASSESSMENT (FOOD AND DRINKING WATER)

The chronic aggregate risk assessment takes into account exposure estimates from dietary consumption of cyazofamid (food and drinking water). The results of the dietary exposure analyses are summarized in Table 9. Chronic aggregate dietary risk (food only) estimates are below the Agency's level of concern. For the chronic analysis, the most highly exposed population subgroup and the highest risk estimate was for Children 1 to 2 years old. The chronic exposures for Children 1 to 2 years old are 0.004778 mg/kg/day for DEEM-FCID™ or 0.004529 mg/kg/day for Lifeline™, which utilize <1.0% (for both DEEM-FCID™ and Lifeline™) of the chronic PAD for cyazofamid.

Table 9. Chronic Aggregate Exposures to Cyazofamid						
Population Subgroup	**cPAD (mg/kg/day)**	**Chronic Food Exposure[1] (mg/kg/day)**	**Maximum Chronic Water Exposure[2] (mg/kg/day)**	**Ground Water EDWC [3] (ppb or µg/L)**	**Surface Water EDWC [3] (ppb or µg/L)**	**Chronic DWLOC[4] (ppb or µg/L)**
General U.S. Population	0.95	0.001016	0.95			3.3×10^4
All Infants (< 1 year old)	0.95	0.001501	0.95			9.5×10^3
Children 1-2 years old	**0.95**	**0.004778**	**0.95**			**9.5×10^3**
Children 3-5 years old	0.95	0.003236	0.95			9.5×10^3
Children 6-12 years old	0.95	0.001338	0.95	**0.495**	**8.085**	9.5×10^3
Youth 13-19 years old	0.95	0.000589	0.95			2.8×10^4
Adults 20-49 years old	0.95	0.000751	0.95			3.3×10^4
Adults 50+ years old	0.95	0.000802	0.95			3.3×10^4
Females 13-49 years old	0.95	0.000816	0.95			2.8×10^4

[1] The exposure from the model producing the highest exposure estimate for the population subgroup was used.
[2] Maximum Water Exposure (mg/kg/day) = cPAD (mg/kg/day) - Dietary (Food) Exposure
[3] The highest level was used.
[4] $\text{DWLOC}(\mu g/L) = \frac{[\text{maximum water exposure (mg/kg/day)} \times \text{body weight (kg)}]}{[\text{water consumption (L)} \times 10^{-3}\ \text{mg}/\mu g]}$

A body weight of 70 kg is assumed for adults, 60 kg for females and youth, and 10 kg for children; water consumption is assumed to be 2L for adults and 1L for children.

As shown in Table 9, the resulting dietary food exposures are <1% of the Chronic PAD for all population subgroups included in the analysis. The results of this dietary exposure analysis should be viewed as very conservative and health protective. Refinements such as use of percent crop-treated information and/or anticipated-residue values would yield even lower estimates of chronic dietary exposure.

The EDWCs used to assess chronic aggregate dietary risk are 0.495 µg/L (for ground water, based on SCI-GROW) and 8.085 µg/L (in surface water, based on FIRST modeling, annual average). The back-calculated DWLOCs (Table 9) for assessing chronic aggregate dietary risk range from 9,500 µg/L for the population subgroup with the highest food exposure (Children 1 to

2 years) to 33,000 µg/L for the subgroups U.S. Population, Adults 20 to 49 years old, and Adults 50+ years old.

The chronic EDWCs are less than the Agency's level of comparison (the DWLOC value for each population subgroup) for cyazofamid residues in drinking water as a contribution to chronic aggregate exposure. The Agency concludes with reasonable certainty that residues of cyazofamid in drinking water will not contribute significantly to the aggregate chronic human health risk, and that the chronic aggregate exposure from cyazofamid residues in food and drinking water will not exceed the Agency's level of concern (100% of the chronic PAD) for chronic aggregate exposure by *any* population subgroup. EPA generally has no concern for exposures below 100% of the chronic PAD, 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. This risk assessment is considered high confidence, very conservative, and very protective of human health.

CANCER AGGREGATE RISK ASSESSMENT

The Agency classified cyazofamid as "not likely to be carcinogenic to humans". Thus, an aggregate cancer risk assessment was not performed for cyazofamid.

CUMULATIVE RISK

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 cyazofamid and any other substances and cyazofamid does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that cyazofamid 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/.

OCCUPATIONAL AND RESIDENTIAL RISK ASSESSMENT

RESIDENTIAL EXPOSURE/RISK PATHWAY – There are no non-agricultural use sites associated with the proposed uses; it is assumed that RANMAN™ 400SC is not intended for residential vegetable gardens. Therefore, a residential risk assessment for cyazofamid was not conducted.

OCCUPATIONAL HANDLER – All combined MOEs are above 100 (when gloves are added for mixing/loading liquid for aerial application to potatoes), and therefore, are not of concern.

OCCUPATIONAL POSTAPPLICATION – Risk calculations for postapplication workers

result in MOEs ranging from 5,100 to 64,000 on the day of application. Because the MOEs are greater than the target MOE of 100, these risks do not exceed the Agency's level of concern for postapplication workers.

The minimum REI required under the Worker Protection Standard (WPS), based on the acute toxicity categories for cyazofamid, is 12 hours.

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

ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS

FATE AND TRANSPORT PROCESSES

The fate of cyazofamid was evaluated by considering data on its stability to both hydrolysis and photolysis and its degradation processes in aqueous phases as well as soil and field environments. Cyazofamid is short-lived in the systems examined, it appears to be highly affected by photolysis followed by aerobic soil degradation and hydrolysis. See Table 10 for details.

The main process involved in the fate of cyazofamid in aqueous systems is photolysis followed by hydrolysis. Its fate in soil as well as its limited mobility in soil environments appears to be controlled by biotic degradation as well as its strong affinity for adsorption to the soil. Cyazofamid is not persistent or mobile in the environment. The combined data on cyazofamid and its degradates indicate that the terminal major degradation products are CCIM and CTCA. CTCA is expected to be the terminal persistent/mobile degradate in soils and therefore may contaminate groundwater by leaching or surface water by run-off. In contrast, CCIM is expected to be the major terminal degradate in water bodies with low biological activity because it expected to form in the system mainly as a result of abiotic hydrolysis of the parent and is stable to hydrolysis.

Table 10. Cyazofamid environmental fate data summary

Parameter	Value[1]
Hydrolysis	$t_{½}$ ~ **11.9 days** @ 25ºC, pH 4; $t_{½}$ ~**12.9 days** @ 25ºC, pH 5 $t_{½}$ ~ **11.9 days** @ 25ºC, pH 7; $t_{½}$ ~**10.8 days** @ 25ºC, pH 9 $t_{½}$ ~ **13.4, 12.4, 11.2, 8.5 hrs** @ 50°C, pH's 4, 5, 7, 9, respectively **Major degradates** (of the recovered)**:** CCIM (74-83%) and CCIM-AM (9-10% only at pH 9)
Photolysis in water at pH 5	$t_{½}$ ~ **30 Minutes** **Major degradates**: CCTS (37.9% at 0.13 day), CCIM (39.6% at 0.25 and 2 days), HTID (18.5% at 21 days), and CDTS (9.6% at 36 days). The degradate p-Toluamide(12.1% at 36 days) was identified only in the [benzene-^{14}C]cyazofamid.
Aerobic soil metabolism	$t_{½}$ = **6.1-6.4 days** in a loamy sand soil from Ohio, **Soil 1** (pH 6.5, %OC 0.66) **Major degradates:** CCIM, CCIM-AM, and CTCA
	$t_{½}$ = **3.7-4.0 days** in a Sandy loam soil from England, **Soil 2** (pH 7.6, %OC= 1.2) $t_{½}$ = **4.3-4.4 days** in a Sandy loam soil from England, **Soil 3** (pH 6.9, %OC= 3.0) $t_{½}$ = **4.9-6.0 days** in a Sandy soil from Germany, **Soil 5** (pH 5.9, %OC= 0.63) **Major degradates:** CCIM, CCIM-AM and CTCA
Aerobic aquatic metabolism	$t_{½}$ = **14.7- 18.0 days** (total system): river water/Sandy loam (~3:1) $t_{½}$ = **9.5- 10.9 days** (total system): creek water/Sandy loam (~3:1) **Major degradates:** CCIM (up to 47%), CTCA (up to 31%), and CCIM-AM (up to 11%)
Anaerobic aquatic metabolism	$t_{½}$ = **5.6-6.2 Days** (total system): Milli-Q water/Sandy loam (~2:1) **Major degradates** (of the applied)**:** CCIM (25%), CCIM-AM (17%); CTCA (22%)
Adsorption/ Desorption (K_d and $\mathbf{K_{oc}}$ in L Kg^{-1})	[Imidazole-4-^{14}C]/[Benzene-U-^{14}C]: Loamy sand (Ohio), **Soil 1**: K_d = 9.99/ 6.96 and $\mathbf{K_{oc}}$**= 1,524/1,062** Sandy loam (UK), **Soil 2**: K_d = 43.31/87.00 and $\mathbf{K_{oc}}$**= 1,444/2,900** Sandy loam (UK), **Soil 3**: K_d = 14.11/13.49 and $\mathbf{K_{oc}}$**= 1,176/1,124** Sand (Germany), **Soil 5**: K_d = 5.14/ 4.14 and $\mathbf{K_{oc}}$**= 815/ 657**
Mobility in Soils: Column Un-aged Leaching (4 soils)	> 98% of the applied radioactivity remained on the top 10 cm with very limited leaching. Observed rate and pattern of degradation were similar to aerobic soil (Major degradates: CCIM, CCIM-AM). Leachate constituted <0.3% of the applied radioactivity.

Table 10. Cyazofamid environmental fate data summary		
Parameter		Value[1]
Mobility in Soils: Aged Leaching (one soil)		> 95% of the radioactivity remained on the top 10cm with very limited leaching. Observed rate and pattern of degradation were similar to aerobic soil (Major degradates: CCIM, CCIM-AM, and minor degradate CTCA). Leachate constituted nearly 1% of the applied radioactivity and was dominated by only one degradate: CTCA. In comparison with unaged soils, radioactivity profile indicated aging may have caused an increase in mobility.
Terres-trial Field Dissip a-tion	WA	**DT_{50} = 1.3 days** in bare loamy sand soil (pH 6.5, %OM=0.60) in Grant County
	NY	**$t_{½}$ = 2.0 days** in bare sandy loam soil (pH 6.1, %OM=3.33) in Wayne County
	GA	**DT_{50} = 2.0 days** in bare loamy soil (pH 6.2, %OM=0.55) in Montezuma
	CA	**$t_{½}$ = 3.6 days** in bare loamy soil (pH 6.5, %OM=2.38) in Watsonville
Storage Stability		Interim report indicate acceptable frozen storage stability for 250 days for cyazofamid and its degradates CCIM, CCIM-AM and CCBA. No clear pattern of degradation appeared during storage. The degradate CTCA appeared to degrade slightly during storage.
Accumulation in Fish: Invalid study		

[1] **Soil 1**: Loamy Sand, Ohio (pH 6.5, %OC= 0.66); **Soil 2**: Sandy loam, England (pH 7.6, %OC= 1.2); **Soil 3**: Sandy loam, England (pH 6.9, %OC= 3.0); **Soil 4:** Loamy sand, England (pH 7.6, %OC= 1.1); **Soil 5:** Sandy soil, Germany (pH 5.9, %OC= 0.63).

FATE AND TRANSPORT OF MAJOR CYAZOFAMID DEGRADATES

The major degradates CCIM, CCIM-AM and CTCA are all fairly resistant to hydrolysis. CCIM and CCIM-AM degrade rapidly in soil under aerobic conditions with half lives under 12 days; CTCA degrades very slowly in soil. Available fate data on cyazofamid major degradates CCIM, CCIM-AM and CTCA, are presented in Table 11.

Table 11. Environmental fate data summary for the major degradates of cyazofamid				
Parameter[1, 2, 3]		Value ($t_{½}$ for [phenyl-U-^{14}C] for [imidazole-4-^{14}C])		
		CCIM	CCUN-AM	CTCA
Hydrolysis		All three were relatively stable @ 50°C for 5 days in pHs 4, 7, and 9.		
Aerobic soil metabolism	**Soil 3**	**$t_{½}$ = 1.4 - 1.3 days**	**$t_{½}$ = 6.3 - 6.6 days**	**$t_{½}$ >120 days** (relatively stable) in all three soils
	Soil 4	**$t_{½}$ = 1.3 - 0.9 days**	**$t_{½}$ = 10.0 - 6.6 days**	
	Soil 5	**$t_{½}$ = 2.9 - 2.6 days**	**$t_{½}$ = 20.2 - 12.3 days**	
	Major degra-dates	CCIM-AM, CTCA, CCBA-AM.	CTCA (max. 49.5-57.4% of the applied)	None identified
Adsorption/ Desorption (K_d and **K_{oc}** in L Kg^{-1}) Using: [Benzene-U-^{14}C]	**Soil 1**	K_d= 3.91 **K_{oc}= 594**	K_d= 22.43 **K_{oc}= 3,398**	K_d= 8.96 **K_{oc}= 1,357**
	Soil 2	K_d= 5.70 **K_{oc}= 475**	K_d= 23.30 **K_{oc}= 1,941**	K_d= 9.80 **K_{oc}= 816**
	Soil 3	**K_d=** 23.57 **K_{oc}= 786**	**K_d=** 62.47 **K_{oc}= 2,082**	**K_d=** 17.16 **K_{oc}= 572**
	Soil 5	**K_d=** 7.3 **K_{oc}= 1,158**	**K_d=** 13.64 **K_{oc}= 2,165**	**K_d=** 3.77 **K_{oc}= 599**

[1] **Soil 1**: Loamy Sand, Ohio (pH 6.5, %OC= 0.66); **Soil 2**: Sandy loam, England (pH 7.6, %OC= 1.2); **Soil 3**: Sandy loam, England (pH 6.9, %OC= 3.0); **Soil 4:** Loamy sand, England (pH 7.6, %OC= 1.1); and **Soil 5:** Sandy soil, Germany (pH 5.9, %OC= 0.63).

[2] Laboratory and fate data were from mostly supplemental studies. Complete characterization of the fate of cyazofamid requires data to show that no parent or degradate were left as part of the bound residue and to characterize various other components that may be present.

[3] The registrant is required to respond to notes present in the Agency's data evaluation review of the submitted environmental fata studies. The registrant must submit additional details concerning the methods and/or results as well as clarifications of the data for the direct photolysis in water study. New studies are required for photolysis on soil, aerobic soil metabolism (only for two soils from use relevant US soils); aerobic aquatic metabolism (only for one water sediment system), anaerobic aquatic metabolism (only for one water sediment system), adsorption/desorption studies (only for two soils from use relevant US soils), and accumulation in fish studies. Following the registrants' response on the bound residue issue and the availability of a method with reasonable limit of quantification for field samples. The Agency may request new field dissipation studies to be conducted.

ENVIRONMENTAL RISK ANALYSIS

Toxicity Endpoints for Ecological Effects Analyses

Based on ecological effects data, the toxicity endpoints used in the assessment of cyazofamid can be characterized as follows:

- Avian acute oral - Practically non-toxic (LD50= >2000 mg/Kg)
- Avian acute dietary - Practically non-toxic (LC50= >4740 ppm)
- Avian chronic (reproduction)- (no NOAEC was established, LOAEC 168 ppm)
- Mammalian acute oral - Practically non-toxic (LD50 >5000 mg/Kg)
- Mammalian chronic (reproduction)-(NOAEL= 20,000 ppm)
- Honey bee acute - Practically non-toxic (LD50= >100 µg ai/bee)
- Fish (freshwater) acute - (LC50= >0.10 ppm due to limited solubility)
- Fish (freshwater) chronic - Reduced growth (33 day NOAEC=0.0901 ppm)
- Invertebrate (freshwater) acute - (48 hr LC50= >1.3 ppm) (Limited cyazofamid's solubility)
- Invertebrate (freshwater) chronic- (21-day NOAEC= 0.11 ppm, no effects)
- Fish (estuarine) acute - (96 hr LC50= >0.167 ppm)
- Invertebrate (estuarine) acute - (96 hr LC50/EC50= 89 ppb for mysid and 14.7 ppb for mollusc)
- Plants - (EC50 = 33 ppb for aquatic plants)(No terrestrial species affected at 0.0728 lb a.i./A)

Bird and Mammal Overview. - Cyazofamid is practically non-toxic to birds and mammals on an acute basis. There are uncertainties regarding chronic risk to avian species due to a lack of valid data. The Agency will calculate RQs for chronic avian risk once new data are submitted and reviewed. However, at the present time, we are using the submitted supplemental data from both Bobwhite and Japanese quail to characterize possible effects. No acute or chronic LOC's were exceeded for mammals.

Avian Species (Acute Oral, Subacute Dietary and Reproduction). - For single and multiple applications, avian acute LOCs are not exceeded at the maximum use rate. Based on the data currently available to the Agency, there are no definitive avian reproduction risks below the Agency's level of concern. However, two of the three available avian reproduction studies, for the Bobwhite Quail and the Japanese quail, show some evidence of reproductive affects. In addition neither quail study elicited a definitive NOAEC nor a normal dose response. To address these issues the agency is requiring a new Bobwhite Quail study. The Agency will reevaluate the uses when that study is received and reviewed.

Mammalian Species (Acute Oral and Reproduction). - In toxicity studies conducted on laboratory rats, cyazofamid was practically non-toxic to small mammals on an acute oral basis (LD_{50} of >5000 mg/kg). The degradates were moderately to practically non-toxic (LD_{50} values ranged from 324 mg/Kg for CCIM to >3000 mg/Kg for CCIM-AM). In a developmental toxicity

study there were no effects to New Zealand white rabbits or to rats from exposure to technical cyazofamid. Results from a 2 generation chronic reproduction study indicate reproductive toxicity at a LOAEL of >20,000 ppm (NOAEL of 20,000 ppm) with no toxic reproductive endpoints affected. No acute or chronic LOC were exceeded from the use of cyazofamid.

Freshwater fish. - In acute toxicity studies conducted on cold-water and warm-water species, the 96-hour LC_{50} values for the technical grade material were not reliable for freshwater fish on an acute basis due to the limited solubility of the compound and poor recoveries of the compound. Although some of the aquatic eco-toxicity studies were deemed supplemental or invalid, risk was evaluated up to the limit of solubility resulting in low risk. The limit of solubility for cyazofamid and its degradates CCIM, CCIM-AM and CTCA was assumed to equal 0.107 ppm (parent solubility). An early life-stage toxicity test conducted on fathead minnow showed that cyazofamid significantly affected larval growth (length) at the concentration of 0.179 ppm (LOAEC) with no effects (NOAEC) occurring at 0.0901 ppm. No acute or chronic LOC were exceeded from the use of cyazofamid.

Freshwater invertebrates. - In an acute study, the test substance was observed undissolved as a surface film in the 0.45 ppm test solutions and undissolved as surface film and bottom deposit in the 0.79 and 1.3 ppm test solutions. The study author reported that the concentrations tested in this experiment exceeded the water solubility of cyazofamid by a factor of 10 and that the solubility of test substance in this experiment was greatly limited despite attempts at centrifugation and filtration. After 48 hours, no mortalities or sub-lethal effects were observed. In the chronic study, there were no statistically significant treatment related mortalities. No acute or chronic LOC were exceeded from the use of cyazofamid.

Estuarine/Marine fish. - Since the LC50 is >0.167 ppm, the toxicity of technical cyazofamid can be categorized as highly toxic to estuarine/marine fish on an acute basis. There was a 15% mortality rate observed on day 4 of exposure in the 0.167 ppm group with the NOAEC as 0.108 ppm. The limit of water solubility is 0.14 ppm. No acute LOC's were not exceeded for marine fish. Summary chronic data indicate that chronic LOCs will not be exceeded.

Estuarine/Marine invertebrates. - Since the LC50/EC50's are 0.0147 and 0.089 ppm, the toxicity of technical cyazofamid can be categorized as very highly toxic to estuarine/marine invertebrates on an acute basis. Most acute LOC's were not exceeded for marine invertebrates. Chronic data were not required. An RQ of 0.30 exceeded the acute endangered species LOC of 0.05 for estuarine/marine invertebrates should the compound enter aquatic habitats where these organisms live. These RQ values were based on a multiple application scenario of 10 consecutive applications at 7-day intervals and thus risk is very likely below the LOC. Nevertheless, there are no endangered estuarine/marine invertebrates listed Summary chronic data indicate that LOCs will not be exceeded.

Beneficial Insects. - Cyazofamid is practically non-toxic to bees on an acute contact (LD_{50} > 100 µg ai/bee) and acute oral (LC_{50} > 151.7 µg ai/bee) basis. Low risk is expected based on the very low acute toxicity to bees.

Toxicity to Plants. - Seedling emergence was studied on 11 plant species after application of cyazofamid, at a single rate of 0.0727 lb a.i./A. The EC_{25} and NOAEC value for ryegrass emergence is >0.0727 and <0.0727 lb a.i./A. No other species were sensitive to treatment. The EC_{25} and NOAEC values were >0.0727 and 0.0727 lb a.i./A.. Vegetative vigor was studied on 11 plant species. No species showed sensitivity and there were no significant treatment effects on any endpoint or species. The EC_{25} and NOAEC values for lettuce and onion were >0.0703 and 0.0703 lb a.i./A and >0.0728 and 0.0728 lb a.i./A for all other species. Toxicity to the Duckweed (*Lemna gibba*). There were no effects on frond number, growth rate and area under the curve. The NOAEC and EC_{50} were 1,220 and >1,220 ppb, respectively. Non-endangered, non-target and semi-aquatic plants species LOCs are not exceeded from the application of cyazofamid at the maximum use rate.

RISKS TO ENDANGERED SPECIES

There may be a potential for chronic adverse effects on endangered avian species should exposure actually occur, however, since the data are suspect and the studies need to be repeated, these risks are uncertain. Also, there is a possibility of acute risk from the degradate CCIM to endangered small mammals that weigh $\leq$ 15g that eat only short grass under multiple application scenarios to potatoes (RQ of 0.14). CCIM RQ results were based on the assumption of an instant (i.e. upon application) molecular conversion from parent to CCIM (molecular ratio= 0.6702). Thus these results are likely conservative and realistically the RQ for small mammals is very likely below the LOC.

The RQ of 0.30 exceeded the acute endangered species LOC of 0.05 for estuarine/marine invertebrates should the compound and its degradates enter aquatic habitats where these organisms live. These RQ values were based on a multiple application scenario of 10 consecutive applications at 7 day intervals and thus risk is very likely below the LOC. Nevertheless, there are no endangered estuarine/marine invertebrates listed. Also there were no risks to endangered terrestrial and aquatic plants.

ENDOCRINE DISRUPTION

Based on available data, cyazofamid did have reproductive effects on birds. These effects included reductions in 14 day survivors, reductions in eggshell thickness, reductions in # hatched and reductions in female and survivor body-weights. However, EPA is required under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA), to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis 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). When the appropriate screening and or testing protocols being considered under the Agency's Endocrine Disruptor Screening Program have been developed, cyazofamid may be subjected to additional screening and or testing to better characterize effects related to endocrine disruption.

SUMMARY OF DATA GAPS

1) As a condition of registration, the registrant is being required to satisfy data gaps by responding to issues raised in most of the Environmental Fate and Effects Data Evaluation Reports, by submitting additional details about methods and/or results as well as clarifications of the data for the photolysis in water study, and by conducting new studies for photolysis on soil, aerobic soil metabolism, adsorption/desorption, anaerobic aquatic metabolism and accumulation in fish studies.
2) The Agency is also requiring the registrant to submit studies such as hydrolysis/aerobic soil on the degradate CCTS to look into the fate of this degradate and to confirm that the degradates HTID, CDTS and *p*-Toluamide were only photolytic degradates resulting from long exposure to light.
3) Guideline No. 71-4. A replacement avian reproduction studies using bobwhite quail is required to establish valid NOAECs for parent cyazofamid and the CCIM degradate.
4) Guideline No. 74-2(d). Freshwater Invertebrate Life Cycle Test using the parent. In the rejected study there were no statistically significant treatment related mortalities. No growth related parameters were measured during the 3 week study and therefore the study needs to be repeated.
5) Guideline No. 161-3. Photo Degradation on Soil. Study was not acceptable and a replacement study must be submitted.
6) Guideline No. 162-1. Aerobic Soil Metabolism. (Two relevant U.S. soils.)
7) Guideline No. 162-2. Aerobic Aquatic Metabolism. (One water sediment system.)
8) Guideline No. 162-3. Anaerobic Aquatic Metabolism. (One water sediment system.)
9) Guideline No. 162-3. Adsorption/Desorption. (Two relevant U.S. soils.)
10) Guideline No. 165-4. Bio-accumulation in Fish. Study was not acceptable and a replacement study must be submitted.
11) Guideline No. 860.1300 - Nature of the Residue: The registrant must provide information pertaining to dates of sample collection, extraction, and final analysis. Representative chromatograms of the radiolabeled residues taken before and after storage under frozen conditions should be submitted.

12) Guideline No. 860.1380 - Storage Stability: Storage stability data for 18 months on the representative commodities of the cucurbit group is being required to support the storage intervals and conditions of the crop field trials.
13) Guideline No. 860.1850 - Confined Accumulation in rotational Crops: Data are required to

confirm the actual sample storage intervals. Storage stability data indicate that the parent and its metabolites CCIM and CCBA are stable in fortified samples of carrot roots, lettuce, and wheat forage stored frozen for at least 4 months.

PUBLIC INTEREST FINDING

The Agency granted reduced risk status to cyazofamid, and hence registration is considered to be in the public interest.

GOVERNMENT PERFORMANCE AND RESULTS ACT

Registering cyazofamid will meet objectives of GPRA title 3.1.1 by assuring new pesticides entering the market are safe for humans and the environment.

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