United States
Environmental Protection
Agency

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

Pesticide Fact Sheet

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

Description of Chemical

Chemical Name:	N-(2-chloro-4-pyridinyl-N'-phenylurea
Common Name:	Forchlorfenuron (ANSI)
Trade Names:	CPPU, KT-30
Chemical Class:	Phenyl urea
EPA Chemical Code:	128819
Chemical Abstracts Service (CAS) Number:	68157-60-8
Year of Initial Registration:	2004
Pesticide Type:	Plant Growth Regulator
U.S. Producer:	KIM-CL, LLC

Forchlorfenuron is a new plant growth regulator registered for use on grapes raisins, and kiwifruit. Forchlorfenuron is a phenyl urea compound.

USE PATTERN AND FORMULATIONS

Forchloefenuron is a cytokinin, which improves fruit size, fruit set, cluster weight and cold storage in grapes and kiwifruits. Forchlorfenuron acts synergistically with natural auxins to promote plant cell division and lateral growth. This plant growth regulator causes an increase in

berry or fruit size, including varieties not tolerant to gibberellic acid (certain grape varieties and kiwi). Application rates are extremely low. For grapes, lower use rates minimize harvest delay, while the higher use rates of 8 to 10 grams active ingredient (a.i.) per acre (A) maximizes berry size and harvest delay. For kiwi fruit, application rate ranges from 2 to 8 grams a.i./A.

One application is to be made at early post-bloom by ground sprayer, directed to provide thorough coverage to the flowers or developing fruit. For grapes, the lower rates of 0.0044 to 0.013 lb a.i./A minimize harvest delay, and the higher rates of 0.018 to 0.022 lb ai/A maximize berry size and harvest delay. For kiwi fruit, application rate ranges from 0.0044 to 0.018 lb ai/A. Only one application per season is made. Two commercial end-use products are for use on grapes and kiwifruit: ABG-3207 (a 0.07 lb/gallon soluble concentrate), and a 98% crystaline solid.

SUMMARY OF SCIENCE FINDINGS

PHYSICAL/CHEMICAL PROPERTIES

Table 1. Chemical Structure and Nomenclature

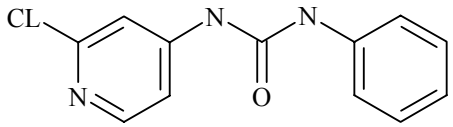
Compound	
Common name	forchlorfenuron, CPPU
IUPAC name	1-(2-chloro-4-pyridyl)-3-phenylurea
CAS name	N-(2-chloro-4-pyridinyl)-N-phenylurea
CAS #	68157-60-8

Table 2. Physicochemical Properties of Forchlorfenuron Technical

Parameter	Value
Melting point/range	165 - 170°C
pH	Not able to determine because of very low water solubility
Density or specific gravity	1.44 g/mL at 21°C
Water solubility	39 ppm
Solvent solubility	17g/100 mL acetone
Vapor pressure	3.5×10^{-5} torr (25°C)

Table 2. Physicochemical Properties of Forchlorfenuron Technical	
Parameter	Value
Dissociation constant (pK_a)	Need to check with TRB. HED didn't include
Octanol/water partition coefficient	K_{ow} = 1,600

Toxicological Characteristics:

Table 3. Acute Toxicity Profile for Technical Forchlorfenuron		
Guideline No./Study Type	RESULTS	Toxicity Category
870.1100 Acute Oral - rat	LD50 (mg/kg bw): M = 4904; F = 4899; Combined = 4918	III
870.1200 Acute Dermal - rabbit	LD50 (mg/kg bw): M = >2000; F = >2000	III
870.1300 Acute Inhalation - rat	LC50 (mg/L): M = >3.0; F = >3.0	IV
870.2400 Primary Eye Irritation- rabbit	Mild eye irritant	III
870.2500 Primary Skin Irritation - rabbit	Non-irritant	IV
870.2600 Dermal Sensitization - guinea pig	Non-sensitizer	N/A

M = male; F = female

Table 4. Toxicity Profile for Forchlorfenuron		
GDLN	STUDY TYPE & DOSE LEVELS	RESULTS
870.3100	13-WEEK FEEDING - RAT ppm = 0, 200, 1000 & 5000 mg/kg/day = M: 0, 16, 79 & 400 F: 0, 17, 84 & 428	NOAEL (mg/kg/day): M ≥ 400, F = 84 LOAEL (mg/kg/day): M = not determined, F = 428: decrease BW, BW gain & food efficiency
870.3150	13-WEEK FEEDING - DOG ppm = 0, 50, 500 & 5000 mg/kg/day = M: 0, 1.8, 16.8 & 162.4 F: 0, 1.8, 19.1 & 188.7	NOAEL (mg/kg/day): M = 16.8, F = 19.1 LOAEL (mg/kg/day): M = 162.4, F = 188.7; decreases (≥ 10%) in BW gain, FC & food efficiency
870.3700	DEVELOPMENTAL TOX - RAT mg/kg/day = 0, 100, 200 & 400	Maternal: NOAEL (mg/kg/day): 200 LOAEL (mg/kg/day): 400: increased incidence of alopecia; decrease in BW & BW gains Develop: NOAEL (mg/kg/day): 200 LOAEL (mg/kg/day): 400: decreased mean fetal BW
870.3700	DEVELOPMENTAL TOX - RABBIT mg/kg/day: 0, 25, 50 & 100	Maternal: NOAEL (mg/kg/day): ≥ 100 LOAEL: not determined Develop: NOAEL (mg/kg/day): ≥ 100 LOAEL: not determined
870.3800	2-GENERATION REPRODUCTION - RAT ppm = 0, 150, 2000 & 7500 mg/kg/day = F_0M: 0, 11, 144 & 544 F_0F: 0, 13, 169 & 701 F_1M: 0, 13, 168 & 829 F_1F: 0, 15, 202 & 926	Parental: NOAEL (mg/kg/day): M = 11/13, F = 13/15 LOAEL (mg/kg/day): 144-202 = decreased FC F_0 & F_1 M; clinical signs of toxicity & lower BW in F_1 M & F and growth retardation in F_1 & F_2 pups Reproduc: NOAEL (mg/kg/day): M = 144/168, F = 169/202 LOAEL (mg/kg/day): 544-926 = increased pup mortality (F_{1a}, F_{1b} & F_{2a}), emaciation in F_{1b}, and decrease in F_2 pups/litter
870.4300	2-YEAR TOXICITY/CARCINOGENICITY - RAT ppm = 0, 150, 2000 & 7500 mg/kg/day = M: 0, 7, 93 & 352 F: 0, 9, 122 & 518	NOAEL (mg/kg/day): M = 7, F = 9 LOAEL (mg/kg/day): M = 93, F = 122 Reduced BW & BW gain & FC; kidney toxicity (M = suppurative inflammation, F = non-suppurative interstitial nephritis) NOT CARCINOGENIC
870.4100	1-YEAR FEEDING - DOGS ppm = 0, 150, 3000 & 7500 mg/kg/day = M: 0, 5, 87 & 195 F: 0, 5, 91 & 246	NOAEL (mg/kg/day): M = 87, F = 91 LOAEL (mg/kg/day): M = 195, F = 246, decreases in BW, BW gains & FC
870.4200	18-MONTH CARCINOGENICITY - MICE mg/kg/day = 0, 10 & 1000 nominal mg/kg/day = M: 0, 10.0 & 991.4 F: 0, 9.9 & 1001.8	NOAEL (mg/kg/day): M = 10.0, F = 9.9 LOAEL (mg/kg/day): M = 991.4, F = 1001.8, decreases in BW & BW gains in M & F NOT CARCINOGENIC

Table 4. Toxicity Profile for Forchlorfenuron		
GDLN	STUDY TYPE & DOSE LEVELS	RESULTS
870.7485	METABOLISM - RAT single gavage dose of 100 mg/kg (elimination kinetics & metabolites) single gavage dose of 100 mg/kg (bile samples)	Recovery of 97% (M & F) by 168 hours. Absorbed dose 72-84%. Urine 62-74%. Feces 16-28%. Biliary excretion, 20-23% in bile. Urine & feces, elimination half-life 13.1-16.2 hours. Analyses identified parent and 6 metabolites in excreta. Parent not in urine and 1-2% in feces. Major metabolite forchlorfenuron sulfate in urine of males (84%) and females (57%). Hydroxy forchlorfenuron (2 isomers) <4% in urine; predominant metabolite in feces (11% males and 18% females). Other metabolites: hydroxy forchlorfenuron-sulfate, methoxy forchlorfenuron-sulfate, forchlorfenuron glucuronide and dihydroxy forchlorfenuron (each<%5). Metabolism of forchlorfenuron in rats: conjugation with sulfate at phenyl ring before (major pathway), conjugation with glucuronide at phenyl ring, methylation of hydroxy group of hydroxy forchlorfenuron-sulfate and hydroxylation of both chloropyridinyl and phenyl rings.
NONE	DETERMINATION OF CONCENTRATION, STABILITY & HOMOGENEITY - RAT & RABBIT DEVELOPMENTAL	Forchlorfenuron in corn oil at 20, 40 & 80 mg/mL or in aqueous methylcellulose at 25, 50 & 100 mg/mL. Same doses as developmental studies Analyses: suitable to upgrade rat & rabbit developmental studies
870.5375	In vitro mammalian cytogenetics assay in Chinese Hamster CHO-KI cells 10, 20, 40, and 80 µg/mL ± S9 activation	No increase in chromosomal aberrations over background ± S9
870.5550	Unscheduled DNA synthesis in primary rat hepatocytes/mammalian cell cultures 0.1 to 30 µg/mL	No increase in unscheduled DNA synthesis
870.5265	*Salmonella*/mammalian activation gene mutation assay 10-1000 µg/plate +S9 2-200 µg/plate -S9	Evidence of a positive response in tester strain TA1535 in absence of S9 at 50, 100, and 200 µg/plate
870.5265	*Salmonella*/mammalian activation gene mutation assay 10-1000 µg/plate +S9 2-200 µg/plate -S9	Evidence of induced mutant colonies over background in tester strain TA1535 in absence of S9

M = male; F = female; BW = body weight; FC = food consumption

METABOLISM: In the rat, forchlorfenuron is rapidly absorbed and metabolized, with half of the radioactivity excreted via the urine and feces within 16 hours of dosing. The parent compound was a small component of radioactivity excreted in urine and feces. The majority of the recovered radioactivity was identified as the conjugate, forchlorfenuron sulfate.

CHRONIC AND SUB-CHRONIC TOXICITY: In subchronic and chronic dog studies, dose-related effects were generally limited to decreased body weight and body weight gains. In

rats, the only organ that appeared to be affected was the kidney, which showed suppurative inflammation in males and non-suppurative interstitial nephritis in females only in a 2-year rat study (LOAEL = 93 mg/kg/day for males and 122 mg/kg/day for females; NOAEL = 7 and 9 mg/kg/day, males and females).

DEVELOPMENTAL AND REPRODUCTION: The only effects observed in a developmental study in rats were increased incidence of alopecia and decreases in maternal and fetal body weights at the highest dose tested (400 mg/kg/day). The NOAEL was 200 mg/kg/day. In a 2-generation reproduction study in rats, the parental NOAEL was 11-13 mg/kg/day with a LOAEL of 144-202 mg/kg/day based on lower body weights. The reproductive/offspring NOAEL was 144-202 mg/kg/day with a LOAEL of 544-926 mg/kg/day based on pup mortality, emaciation, and decrease in pups/litter. Because effects in offspring occurred at the same or higher doses at which effects were observed in the parental animals, there is no evidence of increased qualitative or quantitative susceptibility.

NEUROTOXICITY: No neurotoxicity studies are included in the current database. None of the other studies reviewed indicated any neurotoxicity. No increase in fetus/pup susceptibility was noted, and there was no evidence of mutagenicity, carcinogenicity, or endocrine disruption.

CARCINOGENICITY: Carcinogenicity studies indicated no evidence of an increase in the incidence of tumors in either the rat or the mouse, and forchlorfenuron has been classified as not likely to be a human carcinogen. The following mutagenicity studies were submitted: *in vitro* mammalian cytogenetics assay in Chinese Hamster CHO-KI cells; unscheduled DNA syntheses in primary rat hepatocytes/mammalian cell cultures; *Salmonella*/mammalian activation gene mutation assay; and a repeat of the *Salmonella*/mammalian activation gene mutation assay. There did not appear to be an effect of test article administration on any of the mutagenicity parameters with the following exception: in the *Salmonella typhimurium* reverse gene assay, there was evidence of induced mutant colonies over background in tester strain TA1535 only without S-9 mix (this assay was repeated with the same results). Forchlorfenuron was not assayed for gene mutations in a mammalian cell test system. A review of a 2-year rat feeding study and an 18-month mouse feeding study did not reveal any concern for cancer. Forchlorfenuron was classified as not likely to be a human carcinogen.

ENDOCRINE DISRUPTION: There is no indication of endocrine disruption in the existing toxicology database. EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a 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).

FOOD QUALITY PROTECTION ACT (FQPA) SAFETY FACTOR

The FQPA Safety Factor has been reduced to 1x for all population subgroups including those comprised of infants and children. There are no concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. There is a lack of increased qualitative or quantitative susceptibility in developmental or reproduction studies, and there is a lack of evidence of neurotoxicity in any study. There is an adequate toxicity database for forchlorfenuron. As there was no evidence of neurotoxicity, it is not necessary to require a developmental neurotoxicity study. In addition, data used to evaluate exposure are adequate, and conservative assumptions are being used to evaluate aggregate exposure through food and drinking water. As a result, exposures are probably considerably overestimated.

TOXICOLOGICAL ENDPOINTS

Acute Dietary Endpoint: The RfD is based on a rabbit developmental study. The study NOAEL of ≥100 mg/kg/day is considered to be a conservative dose for acute dietary risk assessment. The NOAEL of 200 mg/kg/day in the rat developmental study supports the assertion that the rabbit developmental study is a conservative endpoint for risk assessment. The acute RfD = 1.0 mg/kg/day.

Chronic Dietary Endpoint: The RfD is based on a 2-year rat feeding study. The NOAEL of 7.0 mg/kg/day and an uncertainty factor (UF) of 100 are based on decreases in body weight/body weight gain/food consumption, as well as kidney toxicity (suppurative inflammation in males; nonsuppurative interstitial nephritis in females) at the LOAEL of 93 and 122 mg/kg/day in males and females, respectively. The chronic RfD = 0.07 mg/kg/day.

Dermal Exposure: For short-term dermal exposure, the NOAEL is 200 mg/kg/day and the LOAEL is 400 mg/kg/day, based on decreases in maternal body weights/body weight gains and a decrease in mean fetal body weights seen in the developmental rat study. Dermal absorption is assumed to be 100% (default; no study). The minimum acceptable MOE is 100. This risk assessment is required if short-term dermal exposures are anticipated. For intermediate-term dermal exposures, the Agency used the 1-year dog feeding study. In this study, the NOAEL was 87 mg/kg/day (in males) and the LOAELs were 195 mg/kg/day (males) and 246 mg/kg/day (females). As a result, the Agency used the NOAEL of 87 mg/kg/day be used for risk assessment. Dermal absorption is assumed to be 100% (default; no study).

Inhalation Endpoint: Other than the acute LC50 study, there are no inhalation studies available for this chemical. The short-term dermal endpoint (based on oral developmental rat study; NOAEL = 200 mg/kg/day) should be used for the short-term inhalation risk assessment. Likewise, the intermediate-term dermal endpoint (based on oral 1-year feeding study in dogs; NOAEL = 87 mg/kg/day) should be used for the intermediate-term inhalation risk assessment.

Table 5. Summary of Toxicological Doses and Endpoints

EXPOSURE SCENARIO	Dose Used in Risk Assessment (mg/kg/day), UF	Special FQPA Safety Factor and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations)	NOAEL assumed to be 100 UF = 100	FQPA SF = 1 aPAD = 1.0 mg/kg/day	Rabbit developmental study- No effects observed

Table 5. Summary of Toxicological Doses and Endpoints			
EXPOSURE SCENARIO	**Dose Used in Risk Assessment (mg/kg/day), UF**	**Special FQPA Safety Factor and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Chronic Dietary (all populations)	NOAEL = 7.0 UF = 100	FQPA SF = 1 cPAD = 0.07 mg/kg/day	2-year rat feeding study. Decreases in body weight, body weight gain and food consumption as well as effects on the kidney at the LOAEL of 93 and 122 mg/ kg/day for males and females, respectively.
Short-Term (Dermal)*	NOAEL = 200	FQPA SF = 1 MOE = 100	Developmental rat study. Decreases in maternal body weights and body weight gains as well as a decrease in mean fetal body weights.
Intermediate-Term (Dermal)*	NOAEL = 87	FQPA SF = 1 MOE = 100	1-year feeding study in dogs. Based on decreases in body weight, body weight gain, and food consumption.
Long-Term (Dermal)	-	Based on the use pattern, long-term exposure will not occur;therefore, a risk assessment was not conducted.	

Table 5. Summary of Toxicological Doses and Endpoints			
EXPOSURE SCENARIO	**Dose Used in Risk Assessment (mg/kg/day), UF**	**Special FQPA Safety Factor and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Short-Term (Inhalation)*	NOAEL = 200	FQPA SF = 1 MOE = 100	Developmental rat study: Same effects as in short-term dermal.
Intermediate-Term (Inhalation)*	NOAEL = 87	FQPA SF = 1 MOE = 100	1-year feeding study in dogs. Same effects as in intermediate-term dermal.
Long-Term (Inhalation)	-	Based on the use pattern, long-term exposure will not occur;therefore, a risk assessment was not conducted.	
Cancer	-	Not likely to be a human carcinogen; **risk assessment not conducted.**	

* Both dermal and inhalation absorption should be assumed to be 100%

DIETARY EXPOSURE

Acute and chronic dietary risk assessments were conducted using the Lifeline Model Version 2.0 and the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. In these analyses, the dietary exposure and risk estimates resulting from food intake were determined for the general U.S. population and various population subgroups. Tolerance level residues and 100% crop treated assumptions were used. DEEM (Version 7.81) default processing factors were used to modify the tolerance values for processed commodities for which separate tolerances are not being established (i.e., all processed commodities except raisins).

The results of the dietary analyses should be viewed as conservative (health protective) risk estimates. Refinements, such as the use of projected market share data and/or anticipated residue values, would yield even lower estimates of dietary exposure.

For acute dietary exposure, residues in food only were used. The Lifeline Model analysis indicated that the U.S. population and all population subgroups had risk estimates that were below 1% of the acute population adjusted dose (aPAD). The most highly exposed population subgroup was Children 1-2 years old, which had a risk estimate of 0.08% of the aPAD. The general U.S. population utilized 0.02% of the aPAD. The results of the DEEM-FCID analysis

were comparable to those of the Lifeline analysis.

In the chronic dietary exposure analysis, drinking water concentrations were included directly in the assessment. For drinking water, the highest 1-in-10 year chronic value (for grapes in New York) from the PRZM-EXAMS analysis was used as a point estimate. From the Lifeline Model, the U.S. population and all population subgroups had risk estimates that were below 1% of the chronic population adjusted dose (cPAD). The most highly exposed population subgroup was children 1-2 years old, which had a risk estimate of 0.3% of the cPAD. The general U.S. population utilized 0.05% of the cPAD. The results of the DEEM-FID analysis were comparable to those of the Lifeline analysis.

DRINKING WATER EXPOSURE

The Agency conducted a Tier 2 assessment for the Estimated Drinking Water Concentrations (EDWCs) to estimate forchlorfenuron levels in surface water. The models were based on maximum application rates for grapes. The modeling was conducted for parent, the only residue of concern in water. For drinking water, the 1-in-10 year chronic value from the PRZM-EXAMS model was used for the drinking water concentration. The resulting EDWC of 0.32 ppb was used in the aggregate risk assessment. The Agency used the SCI-GROW (groundwater) model to estimate EECs of 0.003 ppb, a value is considerably lower than the surface water values. Consequently the higher value was used in the risk assessment.

AGGREGATE RISK ASSESSMENT (Food and Drinking Water)

Acute aggregate risk is comprised of food and water exposures only. Drinking water monitoring data were not available for forchlorfenuron; therefore, the contribution of drinking water to forchlorfenuron dietary exposure is being considered through the use of drinking water levels of comparison (DWLOCs). The DWLOCs for the general U.S. population and all population subgroups are considerably greater than the EDWCs. As a result, aggregate acute exposure to forchlorfenuron in food and drinking water is below the Agency's level of concern for the general U.S. population and all population subgroups. The DWLOC calculations are summarized in Table 6.

Table 6. Drinking Water Levels of Comparison for Forchlorfenuron

Population Subgroup	aPAD, mg/kg bwt/day	Exposure, mg/kg bwt/day		Concentration, µg/L		
		Acute Food Exposure	Max. Allowable Water Exposure[1]	Ground Water EDWC (ppb)	Surface Water EDWC (ppb)	Drinking Water Level of Comparison[2] (ppb)
U.S. Population	1.0	0.000157	0.999843	0.003	0.54	35,000
All Infants (<1 Year)		0.000526	0.999474	0.003	0.54	10,000
Children 1-2 Years		0.000846	0.999154	0.003	0.54	10,000
Children 3-5 Years		0.000557	0.999443	0.003	0.54	10,000
Children 6-12 Years		0.000217	0.999783	0.003	0.54	10,000
Youth 13-19 Years		0.000089	0.999911	0.003	0.54	30,000
Adults 20-49 Years		0.000101	0.999899	0.003	0.54	35,000

Table 6. Drinking Water Levels of Comparison for Forchlorfenuron						
		Exposure, mg/kg bwt/day		Concentration, µg/L		
Population Subgroup	aPAD, mg/kg bwt/day	Acute Food Exposure	Max. Allowable Water Exposure[1]	Ground Water EDWC (ppb)	Surface Water EDWC (ppb)	Drinking Water Level of Comparison[2] (ppb)
Adults 50+ Years		0.000105	0.999895	0.003	0.54	35,000
Females 13-49		0.000112	0.999888	0.003	0.54	30,000

[1] Maximum Allowable Water Exposure = PAD - sum of all quantifiable exposures.
[2] Drinking Water Level of Comparison = Maximum Allowable Water Exposure × Body Weight (10 kg infants and children, 60 kg females, 70 kg all others) × 1000 µg/mg ÷ Consumption (1 L/day infants and children, 2 L/day all others).

Chronic (non-cancer) aggregate risk is the sum of exposures resulting from chronic dietary food + chronic drinking water + chronic residential uses. However, forchlorfenuron has no registered or proposed residential uses. In the Lifeline and DEEM-FID. analyses, the estimated forchlorfenuron concentrations in drinking water were included directly in the assessments. As a result, the aggregate chronic assessment is equivalent to the chronic dietary assessment. From the Lifeline Model, the U.S. population and all population subgroups had risk estimates that were below 1% of the chronic population adjusted dose (cPAD), including residues in drinking water. The most highly exposed population subgroup was Children 1-2 years old, which had a risk estimate of 0.3% of the cPAD. The general U.S. population utilized 0.05% of the cPAD. The Agency concludes that the chronic aggregate exposure from forchlorfenuron residues in food and drinking water will not exceed the Agency's level of concern (100% of the cPAD) for chronic dietary aggregate exposure by the general U.S. population or any population subgroup. The results of the assessment using the DEEM model were comparable.

CANCER ASSESSMENT

As forchlorfenuron was classified as not likely to be a human carcinogen, an aggregate cancer exposure analysis was not required.

OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK

Workers may be exposed to forchlorfenuron during mixing, loading, application, and postapplication activities for the proposed crops (grapes and kiwifruit) as well as those crops with Experimental Use Permits (EUPs) in place (apples, blueberries, cranberries, figs, pears, plums, olives, and almonds).

Forchloruron is applied by ground boom or airblast equipment at rates ranging from 0.018 to 0.033 lb ai/acre. Handlers may be exposed to forchlorfenuron during mixing, loading, and application activities associated with agricultural crops. Based on the proposed use patterns, short- and intermediate-term dermal and inhalation exposure are expected to occur.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted to the Agency in support of forchlorfenuron registration, so exposures were estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1.

Because the toxicity endpoints are similar for dermal and inhalation, exposure from these two routes are combined to provide an estimate of total risk, using the reciprocal Margin of Exposure (MOE) approach. Short-term exposures were evaluated against a NOAEL of 200 mg/kg/day and intermediate-term exposures were evaluated against a NOAEL of 87 mg/kg/day. For both scenarios, the target MOE of occupational handlers is 100. For mixer/loaders, estimated total (dermal + inhalation) short-term risks ranged from1600 for mixing/loading wettable powders for groundboom application in blueberries and cranberries to 260,000 for mixing/loading dry flowable formulations for airblast application in kiwifruit. For mixer/loaders, estimated total (dermal + inhalation) intermediate-term risks ranged from790 for mixing/loading wettable powders for groundboom application in blueberries and cranberries to 120,000 for mixing/loading dry flowable formulations for airblast application in kiwifruit. For applicators, estimated total (dermal + inhalation) short-term risks ranged from 25,000 for application with airblast equipment in apples to 460,000 for application with groundboom equipment in grapes. For applicators, estimated total (dermal + inhalation) intermediate-term risks ranged from 13,000 application with airblast equipment in apples to 240,000 for application with groundboom equipment in grapes.

POSTAPPLICATION EXPOSURE

The Agency believes that there are potential exposures to persons entering treated sites (e.g., pruners, harvesters) after application. Postapplication inhalation exposures are not expected, so dermal exposures during postapplication activities were estimated using dermal transfer coefficients and dislodgeable foliar residue values. MOEs for short-term postapplication exposures range from 3,000 for girdling, turning and tying canes in grape vines to 74,000 for hand weeding, irrigating and hedging kiwifruit. MOEs for intermediate-term postapplication exposures range from 1,300 for girdling, turning and tying canes in grape vines to 32,000 for hand weeding, irrigating and hedging kiwifruit. The postapplication exposure MOEs are greater than the target MOE of 100 and therefore do not exceed the Agency's level of concern.

Ecological Effects/Environmental Fate Characteristics:

Adequate environmental fate and ecological toxicity data and Tier I terrestrial/aquatic plant studies were submitted for most of the required species.

Hydrolysis -- Forchlorfenuron, at a nominal concentration of 30 ppm, was hydrolytically stable in pH 5, 7 and 9 aqueous buffer solutions incubated at 25°C for up to 30 days. Following the incubation period, 97.5%, 96.5%, and 96.2% of the applied radioactivity was present as parent compound at pH 5, 7 and 9, respectively.

Photolysis – Forchlorfenuron, at a concentration of 6.7 µg/mL, was photolytically stable in pH 5 aqueous buffer solution that was continuously irradiated with a xenon arc lamp and maintained at 25 ± 1°C for up to 30 days. In the non-sensitized, irradiated solution, the parent compound was initially present at 94.2% of the applied radioactivity and decreased to 80.7-83.7% of the applied at 23-30 days posttreatment. In the dark control solutions, the parent compound was initially present at 94.2% of the applied radioactivity and was 92.7% at 30 days posttreatment. In the sensitized irradiated solutions, the half-life was 5 days.

Metabolism – Forchlorfenuron, at a nominal application rate of 10 µg/g, was essentially stable in sandy loam soil adjusted to 70-75% of 0.33 bar moisture content and incubated in darkness at 25°C for up to 12 months. The calculated half-lives for extractable residues were 578 days

and 1659 days for the sum of extractable and bound, respectively. The parent compound appeared to be relatively stable at 2 to 9 months posttreatment, followed by a slight decrease (61% to 55%) in parent by 12 months. No degradates other than CO_2 were detected. Nonextractable residues were 16.6% of the applied radioactivity at 3 months posttreatment and were a maximum of 23.6% of the applied at 12 months; residues associated with the fulvic acid, humic acid and humin fractions were 34.5%, 9.6% and 55.9% of the bound residues, respectively, at 12 months. Evolved CO_2 was a 0.81-0.95% of the applied at 2-9 months and was 0.061% of the applied at 12 months posttreatment; organic volatiles were negligible. Total cumulative volatiles at 12 months posttreatment accounted for 9.9% of the applied radioactivity.

Sediment/Water Systems - Forchlorfenuron, at a nominal concentration of 10 µg/g, sorbed onto soil and did not degrade significantly based on the sum of extractable, bound, and water residues. The registrant-calculated a half-life of 226 days in anaerobic (nitrogen) flooded sandy loam soil was based on extractable residues. The parent compound appeared to be relatively stable in the water and soil phases from 60 to 90 days posttreatment (anaerobic incubation days 30-60). In the water phase, the parent compound did not exceed 1.6 ppm at any time. Degradates were not detected in the soil or water phases. Nonextractable residues were 13.1% (1.3 ppm) of the applied at 30 days and were a maximum of 30.6% (3.0 ppm) of the applied at 90 days; residues associated with humic acid, fulvic acid and humin fractions were 1.2% (0.025 ppm), 44.3% (0.93 ppm) and 54.3% (1.1 ppm) of the nonextractable radioactivity, respectively, at 90 days posttreatment. Evolved organic volatiles were negligible. The majority of the residues was observed in the soil phase from 30 to 90 days. The soil:water ratio for the parent compound was 10.4:1 at 45 days posttreatment and 3.3:1 to 5.5:1 from 60 to 90 days.

Forchlorfenuron, at a nominal application rate of 10 µg/g, was essentially stable in sandy loam soil adjusted to 70-75% of 0.33 bar moisture content and incubated in darkness at 25 ±1°C for up to 12 months. The calculated half-lives for extractable residues were 578 days and 1659 days for the sum of extractable and bound, respectively. The parent compound appeared to be relatively stable at 2 to 9 months posttreatment, followed by a slight decrease (61% to 55%) in parent by 12 months. No degradates other than CO_2 were detected. Nonextractable residues were 16.6% of the applied radioactivity at 3 months posttreatment and were a maximum of 23.6% of the applied at 12 months; residues associated with the fulvic acid, humic acid and humin fractions were 34.5%, 9.6% and 55.9% of the bound residues, respectively, at 12 months. Evolved CO_2 was a 0.81-0.95% of the applied at 2-9 months and was 0.061% of the applied at 12 months posttreatment; organic volatiles were negligible. Total cumulative volatiles at 12 months posttreatment accounted for 9.9% of the applied radioactivity.

Forchlorfenuron is essentially stable to all routes of dissipation except sensitized photodegradation in water. It is soluble in water to 30 mg/L and essentially non-volatle ($VP=3.5 \times 10^{-10}$torr). It is moderately mobile to essentially immobile soils with Freundlich Kads values of 2-20. Because no data have been submitted for terrestrial field dissipation in the field will follow the conceptual model based on laboratory studies.

Bioaccumulation – Forchlorfenuron accumulation was studied in bluegill sunfish that were exposed to non-radiolabeled and uniformly phenyl ring-labeled [^{14}C]forchlorfenuron at a nominal concentration of 0.10 mg/L under flow-through aquarium conditions. Maximum bioconcentration factors (BCF) were 16x for the viscera tissue and 7.2x for the whole fish tissue samples; a BCF could not be calculated for the fillet tissue because residues were not present above the LOQ (75.3 ppb). Maximum total residues were 1.5 ppm (day 3) and 0.70

ppm (day 21) in the viscera and whole fish tissues, respectively; residues in fish tissues were not characterized. Accumulation plateaus were reached by 1 day in both whole fish and viscera tissues. During depuration >88% of the total residues accumulated by 28 days of exposure were eliminated from the whole fish and viscera tissues by depuration Day-3; residues were not present in fish tissues following depuration Day-1.

Spray Drift - No forchlorfenuron-specific studies were reviewed. The Agency has been working with the SDTF, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency has completed its evaluation of the data base submitted by the SDTF and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessment for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in the spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

ECOLOGICAL CHARACTERISTICS

Avian Acute Oral Toxicity

Avian acute oral studies using the TGAI are required to establish the toxicity of forchlorfenuron to birds. The preferred test species are mallard duck or bobwhite quail. The results of this test are tabulated in Table 7.

Table 7. Forchlorfenuron terrestrial animal toxicity data summary.

Test	Organism	Toxicity
Avian acute oral	Bobwhite quail *Colinus virginianus*	LD_{50} = > 2250 ppm
Avian Subacute dietary	Bobwhite quail *Colinus virginianus*	LC_{50} > 5620 ppm
Avian Subacute dietary	Mallard duck *Anas platyrhynchos*	LC_{50} = >5620 ppm

Mammals, Acute and Chronic

Wild mammal testing is required on a case-by-case basis, depending on the results of lower tier laboratory mammalian studies, intended use pattern and pertinent environmental fate characteristics. In most cases, rat or mouse toxicity values obtained from rat studies substitute for wild mammal testing.

Table 8. Mammalian Toxicity of Forchlorfenuron

Species	Test Type/Classification	Toxicity Value	Affected Endpoints
Rat	Acute Oral LD_{50}	LD_{50} =4918 mg/kg (combined)	not applicable
Rat	2-generation reproduction	Parental NOAEL = 11/13mg/kg/day (♂) 13/15mg/kg/day ( )	
		Parental LOAEL = 144-202mg/kg/day	microscopic lesions in stomach
		Reproductive NOAEL =144/168(M), 169-202,(F) mg/kg/day	increased pup mortality, emaciation, in F1band decrease in pups/litter in F2
		Reproductive LOAEL = 544-926 mg/kg/day	

Freshwater Fish, Acute

Two freshwater fish toxicity studies using the TGAI are required to establish the toxicity of forchlorfenuron to fish. The preferred test species are rainbow trout (a cold water fish) and bluegill sunfish (a warm water fish). Since the LC_{50}s are >9.2 and >8.8 ppm, forchlorfenuron is categorized as moderately toxic to freshwater fish on an acute basis.

Freshwater Fish, Chronic

A fish early life-stage test (Guideline 72-4a) using the TGAI is normally required for a pesticide (e.g., forchlorfenuron) since the following conditions are met: (1) the pesticide is intended for use such that its presence in water is likely to be continuous or recurrent, and (2) forchlorfenuron is expected to be persistent in natural water bodies. However, because of an extremely low application rate and low acute RQ values, chronic effects to fish are unlikely.

Table 9. Forchlorfenuron aquatic animal toxicity data summary.

Test	Organism	Toxicity
Acute freshwater fish	Bluegill sunfish *Lepomis macrochirus*	LC_{50} > 8.8 ppm

Acute freshwater fish	Rainbow trout *Oncorhynchus mykiss*	LC_{50} > 9.2 ppm
Acute freshwater invertebrate	Water flea *Daphnia magna*	EC_{50} = 8.0 ppm (flow through)

Toxicity to Plants

Terrestrial Plants

A Tier I, non-target plant, seedling emergence toxicity study (Guideline 123-1a) using forchlorfenuron was submitted by the registrant. The toxicity of forchlorfenuron to ten terrestrial plant species during seedling emergence was tested. Toxic effects were reported as percent inhibition for the Tier 1 tests. Exposure to forchlorfenuron at the concentration equal to the application rate of 0.055 lbs ai/A (2.5 x of the maximum label rate of 0.022 lbs ai/A) did not cause adverse results equal to or exceeding 25% (Emergence: Inhibition 0-17%; Stimulation 9-26%).

Aquatic Plants – Tier I aquatic plant toxicity studies (Guideline 122-2) were submitted by the registrant. In a 7-day acute toxicity study, freshwater aquatic vascular plants, *Lemma gibba,* were exposed to forchlorfenuron at a single, nominal concentration of 1.0 ppm a.i. and dilution water control under static renewal conditions. The mean measured concentration was 0.90 ppm a.i.. Frond production and growth rate were not inhibited by treatment with Forchlorfenuron. The percent inhibition for mean live fond number was - 4%, compared to the control. The percent inhibition for growth rate was -3%, compared to the control. The EC_{25} for all endpoints was >0.90 ppm a.i..

Terrestrial Insects - Forchlorfenuron is practically non-toxic to honeybees (LD_{50} > 200 µg/bee).

ENVIRONMENTAL RISK SUMMARY

Risk to Aquatic Organisms

Exposure to aquatic non-target organisms is possible through surface water runoff, soil erosion, and off-target spray drift. Aquatic organism exposure predictions are based on a set of standardized water body assumptions (water body size, watershed size, proximity to field, etc.). Expected Environmental Concentrations (EEC's) for forchlorfenuron in the standard farm pond were generated with the Tier II model, Prism/Exams-4. Ground spray scenarios for grapes are single applications of 0.022 lb a.i./acre, or 0.018 lb a.i./acre for kiwi fruit. The acute LC_{50}'s are 8.8 to 9.2 ppm for fresh water fish and 8 ppm for Daphnids. As a result, forchlorfenuron is considered to be moderately toxic to these species on an acute basis. Even though moderate acute toxicity was observed, the acute RQ values for both fish and invertebrates are extremely low (2×10^{-6} to 3×10^{-5}, <<0.05) because of an extremely low application rate of 10 g active ingredient per acre and a limited application method (single ground application). Chronic risk to freshwater fish and invertebrates is also unlikely for the same reasons.

Risk to Avian Species (Acute/Chronic)

Forchlorfenuron is practically non-toxic to terrestrial (birds) on an acute basis. Also, the

screening-level risk assessment indicates that acute Levels of Concern (LOC) for non-target organisms and endangered species are not exceeded, with RQ values ranging from 1 x 10^{-4} to 9 x 10^{-4}. However, the Agency is requesting the avian chronic toxicity study because of observed reproductive effects in a rat study, and the fact that birds are generally more sensitive than mammals.

Mammalian Acute/Chronic (Single application)

The residues expected on mammalian food items after single application of non-granular forchlorfenuron products are based on the highest residue concentrations immediately after application. The results suggest that mammalian acute, restricted use and endangered species levels of concern are not exceeded for all food items.

The mammalian chronic risk quotients for a broadcast application of forchlorfenuron based on rat reproductive toxicity data after a single application of forchlorfenuron were all < 1, based on the highest residue concentrations immediately after application.

The Agency's major concern is forchlorfenuron's persistence and its possible chronic effects to terrestrial organisms. It is highly persistent in the environment with laboratory half-lives ranging from 226-578 days in terrestrial environments and stable in aquatic environments. While forchlorfenuron rapidly photodegrades in sensitized water, the Agency does not believe that this route of dissipation is significant in the environment. Suspended sediment and shading prevent photodegradation.

Environmental Risk Summary:

The studies submitted for this active ingredient are adequate for the screening-level risk assessment. Based on available data, there is no apparent acute risk to aquatic or terrestrial animals, including endangered species. The Agency is also not concerned about chronic risk to aquatic animals because of an extremely low application rate and acute RQ values that were far below any level of concern. However, the Agency is concerned about avian chronic toxicity because of observed reproductive effects in a rat study, and the fact that birds are generally more sensitive than mammals. It is highly persistent in the environment with laboratory half-lives ranging from 226-578 days in terrestrial environments and stable in aquatic environments.

The Agency has conducted a screening level analysis to assess potential ecological risks posed by forchlorfenuron. The exceedance of an RQ does not necessarily indicate "high risk" to a species as the RQ is not an absolute estimate of the likelihood, magnitude, or severity of risk. Inputs into this screening level assessment were designated to overestimate likely exposures and effects of forchlorfenuron. Given the slight exceedences of the RQs and the low use rate and limited use in the U.S. the Agency, believes that potential ecological risks are low.

Agency Public Interest Finding Policy

The Agency has determined that forchlorfenuron will fill a niche for kiwifruit, table grapes, and raisin grapes, and is therefore in the public interest. Since there are no other plant growth regulators available to increase fruit size, the Agency has determined that the criteria for a positive Public Interest Finding have been met for forchlorfenuron on kiwifruit. There are ca. 4800 bearing acres of kiwifruit in California. The harpin protein is registered for kiwi; however, this chemical is not registered in California, where 95 to greater than 98 percent of the U.S. kiwi crop is grown. Other than hydrogen cyanamide, used to stimulate bud burst, there appear to be no other registered plant growth regulators. Forchlorfenuron has been used

through the Experimental Use Permit (EUP) process and has been used to increase fruit size. This plant growth regulator can be used two to three weeks after bloom. The efficacy was rated as fair to excellent. Forchlorfenuron results in an increase in fruit size, but does not affect the number of fruit or the keeping quality of the fruit.

For raisins, the benefits include a decrease in the drying ratio, higher grade fruit, and additional soluble solids in the berry resulting in a heavier raisin. For fresh grapes, the benefits include increased berry size, more uniform berry size within a cluster, firmer berries, less quality loss with long term storage (which may decrease the need for sulfur dioxide gas), and less berry shatter. These factors result in higher yields and higher quality.

GOVERNMENT PERFORMANCE AND RESULTS ACT

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

DATA GAPS

GLN 71-4 a/b, Avian Chronic Study
GLN 122-1b, Aquatic Algal Species
GLN 122-2 , Vegatative Vigor Study
GLN 164-1 Field Dissipation Study

Contact person at USEPA

Mailing address

Dennis McNeilly
Acting Product Manager (22)
Environmental Protection Agency
Office of Pesticide Programs
Registration Division (7505C)
Fungicide Branch
1200 Pennsylvania Avenue NW
Washington, D.C. 20460

Office location and telephone number:

Room 237, Crystal Mall #2
1801 South Bell Street
Arlington, VA 22202
703-308-6742