United States
Environmental Protection Agency
Office of Prevention, Pesticides and Toxic Substances
(7505P)

Pesticide Fact Sheet

Name of Chemical: **Penflufen**
Reason for Issuance: **Unconditional Registration**
Date Issued: **May 2012**

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1. DESCRIPTION OF CHEMICAL

Chemical Name: 1H-Pyrazole-4-carboxamide, N-[2-(1,3- dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-;

CAS Number: 494793-67-8

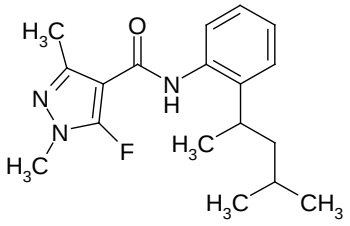
Empirical Formula: $C_{18}H_{24}FN_3O$

IUPAC Name : N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide

Common Name: Penflufen

Experimental Name:	BYF14182
EPA PC Code:	100249
Chemical Class:	carboxamide
Mode of Action:	succinate dehydrogenase inhibitor (SDHI)
Pesticide Type:	Fungicide
U.S. Technical Registrant:	Bayer CropScience P.O. Box 12014, 2 T.W. Alexander Dr Research Triangle Park, NC 27709

Chemical Structure:



2. USE PATTERNS AND FORMULATIONS

Registered Uses: For use on in-furrow and seed piece treatment use on potatoes (tuberous and corm Crop Subgroup 1C), and as a seed treatment for legume vegetables (Crop Group 6 & 7), cereal grains (Crop Group 15 & 16), oilseeds (Crop Group 20) and alfalfa.

Pests/Application Sites: seed borne fungal pathogens

Application Rates: (Seasonal maximum)

Potatoes/other tuberous corm (in furrow app w/seed pieces) – 0.14 lb a.i./acre
Potato seed pieces (treated pieces) – 0.14 lb a.i./acre
Beans (treated seed) – 0.0384 lb a.i./acre
Cereal grains (treated seed) – 0.0078 lb a.i./acre
Wheat (treated seed) – 0.0078 lb a.i./acre
Rice (treated seed) – 0.00645 lb a.i./acre
Corn (treated seed) – 0.0033 lb a.i./acre
Alfalfa (treated seed) – 0.00225 lb a.i./acre
Cotton (treated seed) – 0.0019 lb a.i./acre
Oilseed crop (treated seed) – 0.00123 lb a.i./acre

Do not apply more than 0.143 lb ai/acre per year.

Types of Formulations/
Product Names:

Technical:
Penflufen TC (98.72% a.i.)

End Use (Agricultural Uses):
EverGol Prime (22.7% a.i.)
Penred 240FS (22.4% a.i.)
Emesto Quantum (6.0 % penflufen, 18.6% clothianidin)
Emesto Silver (9.35% penflufen, 1.68% prothioconazole)
EverGol Xtend (13.3% penflufen, 13.3% trifloxystrobin)
EverGol Energy (3.59% penflufen, 7.18% prothioconazole, 5.74% metalaxyl)
Prosper EverGol (0.82% penflufen, 22.3% clothianidin, 0.55% metalaxyl, 0.55% trifloxystrobin)

3. SCIENCE FINDINGS

Physical and Chemical Characteristics:

Available product chemistry data supporting the use of penflufen are summarized below in Table 1.

Table 1. Physiochemical Properties of Technical Grade Penflufen

Parameter	Value
Melting point/range (°C)	111
pH	6.7 (1% suspensions in distilled water at 22°C)
Density (g/mL at 20°C) (relative density compared to water at 4°C, D_4^{20})	1.21
Water solubility (20°C)	Distilled Water at pH 6.5 12.4 mg/L pH 4 11.0 mg/L pH 7 10.9 mg/L pH 9 11.2 mg/L
Solvent solubility (20°C)	Methanol g/L 126.0 g/L n-Heptane 1.6 g/L Toluene 62.0 g/L Dichloromethane >250.0 g/L Acetone 139.0 g/L Ethyl Acetate 96.0 g/L Dimethyl Sulfoxide 162.0 g/L
Vapor pressure	9.0×10^{-9} torr at 25ºC
Dissociation constant, pK_a	No dissociation constant pKa was found in an aqueous solution of penflufen (99.2%) in the range of $1 < pH < 12$. The molecule has no structural moieties which are prone to dissociate.
Octanol/water partition coefficient, $Log(K_{OW})$ (25ºC)	pH 7 = 3.3

4. HUMAN HEALTH EXPOSURE AND RISK ASSESSMENT

Metabolism Assessment:

Penflufen was very extensively metabolized in the rat and numerous metabolites were identified. Unchanged parent compound was found only in low percentages of the administered radioactivity. Metabolic reactions were detected in at least 10 different positions of the molecule, and a large number of metabolites were identified. Most of the metabolites were demethylated in the pyrazole ring. Hydroxylation was another major metabolic reaction leading to trihydroxy and dihydroxy compounds, with only a minor part of the metabolites hydroxylated in only a single position. Further oxidation of hydroxy groups yielded ketones or carboxylic acids. A prominent hydroxylation reaction occurred in the 3 position of the alkyl side chain, and the single metabolite, penflufen-3-hydroxy-butyl, was detected in very low amounts. However, many metabolites originating from penflufen-3-hydroxy-butyl were identified, and this metabolite was considered a key intermediate in the rat metabolism. This assumption was supported by the findings of a separate rat ADME study with penflufen-3-hydroxy-butyl, which showed the same metabolic pattern as in the metabolism studies with the parent compound, demonstrating that the rat is systemically exposed to penflufen-3-hydroxy-butyl after administration of penflufen.

Toxicology Requirements-

The toxicology requirements (40 CFR 158.340) for a food use for penflufen are in Table 2.

Table 2. Toxicology Data Requirements

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rat and mouse)	yes	yes
870.3150	Oral Subchronic (dog)	yes	yes
870.3200	21/28-Day Dermal (rat)	yes	yes
870.3250	90-Day Dermal	CR	-
870.3465	28-Day Inhalation	CR	no
870.3700a	Developmental Toxicity (rat)	yes	yes[a]
870.3700b	Developmental Toxicity (rabbit)	yes	yes[a]
870.3800	Reproduction (rat)	yes	yes
870.4100a	Chronic Toxicity (rat)	yes	yes
870.4100b	Chronic Toxicity (dog)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	yes
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Chronic/Carcinogenicity (rat)	yes	yes

Table 2. Toxicology Data Requirements

Test	Technical	
	Required	**Satisfied**
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395 Mutagenicity—Mammalian Erythrocyte Micronucleus	yes	yes
870.5500 Mutagenicity-Bacterial DNA Damage or Repair Test	no	-
870.5550 Mutagenicity- Unscheduled DNA Synthesis	no	-
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Developmental Neurotoxicity (rat)	CR	no
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration (8-hour), i*n vivo* (male rat)	CR	yes
870.7800 Immunotoxicity(rat and mouse)	yes	yes
Non-Guideline:		
Comparative dermal absorption, in vitro (rat and human skin)	no	yes
28-day oral toxicity (rat)	no	yes
28-day oral toxicity (mouse)	no	yes
8-hour dermal penetration, in vivo (male rat)	no	yes

[a]---study acceptable (non-guideline); study is non-guideline since the highest dose tested was not high enough to produce a dose response, which is a criteria for a guideline study; however, ToxSAC did not advise asking for additional studies since the endpoints selected are protective of any developmental effects that may be seen at much higher doses.

Acute Toxicity-

Penflufen Technical is toxicity category IV for acute oral, acute inhalation, and primary skin irritation. It is toxicity category III for acute dermal and primary eye irritation and is a non-sensitizer (Table 3).

Table 3. Acute Toxicity of Technical Penflufen

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute oral toxicity	48023749	LD50 = >5000 mg/kg	IV
870.1200	Acute dermal toxicity	48023750	LD50 >2000 mg/kg	III
870.1300	Acute inhalation toxicity	48023801	LC50 >2.02 mg/L	IV
870.2400	Acute eye irritation	48023802	At 24 hrs. conjuctival redness score of 2 in 2/3 rabbits and some swelling in one rabbit. All eyes returned to normal after 72 hours.	III
870.2500	Primary skin irritation	48023803	No dermal irritation, clinical signs or body weight loss	IV
870.2600	Dermal sensitization	48438301	Not a dermal sensitizer	Negative

Subchronic, Chronic and Other Toxicity-

The liver and thyroid are target organs for penflufen. Increased liver weight, alterations in clinical chemistry parameters relevant to effects on the liver, and an increase in the incidence of hepatocellular hypertrophy were consistent findings across species and duration of exposure (28-day, 90-day, and 1- to 2-year exposure periods). The hepatic total cytochrome P-450 content, and benzoxyresorufin (BROD) and pentoxyresorufin (PROD) enzyme activities, were shown to be increased in rats of both sexes following subchronic oral exposure. Additionally, increased incidence of thyroid follicular cell hypertrophy/hyperplasia was observed across studies and species (no data provided on thyroid hormone levels). The liver and thyroid findings were mostly reversible after a 3-month recovery period in the rat. In the rat and mouse, following 104 week/78 week exposure periods at dose levels up to and/or greater than the limit dose, there was no increase in the incidence of liver or thyroid tumors. Decreased motor/locomotor activity was observed in both sexes of rats following acute and in female rats following subchronic oral exposure, although neuropathological lesions were not observed. There are no mutagenicity concerns.

Carcinogenicity-

EPA has classified penflufen as "Suggestive Evidence of Carcinogenic Potential." Quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity that could result from exposure to penflufen.

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
28-Day Oral (feed)/rat	12, 154, 560 (male); 13, 169, 648 (female)	560(male) and 648(female)	Not identified	The liver was identified as a major target organ for BYF 14182 (dose-related increase total P-450, BROD, and PROD activities in both sexes, increased cholesterol levels in females, increased liver weight in both sexes, increased incidence of hepatocellular hypertrophy in both sexes). The liver effects are considered adaptive and not adverse.
28-Day Oral (feed)/ mouse	M: 0, 26, 632, 1274 F: 0, 31, 741, 1585	1274 (male) and 1585 (female)	Not identified	The liver effects (increased liver weights associated with centrilobular hepatocellular hypertrophy; associated clinical chemistry findings at 7000 ppm) are considered adaptive and not adverse.
28-day Oral/ dog/	M: 0, 49, 244, 759 F: 0, 52, 246, 895	759 (male) and 895 (female)	Not identified	No adverse effects (2 Beagle dogs/sex) administered BYF 14182 *via* the diet (28 days); the liver and thyroid were identified as target organs, as evidenced by increased alkaline phosphatase and GGT activities in both sexes, increased liver weight and increased incidences of hepatocellular hypertrophy, thyroid follicular cell hypertrophy, and decreased follicular diameter

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
				in the thyroid in both sexes.
870.3100/ 90-day Oral/rat	M: 0, 9.5, 457, 949 F: 0, 11.4, 492, 1009	949 (male) and 1009 (female)	Not identified	The findings at 14000 ppm included an increase in total cholesterol concentration and gamma-glutamyltransferase activity in both sexes, an increase in the incidence of centrilobular hepatocellular hyper-trophy, which was correlated with higher liver weights and macroscopically enlarged livers in both sexes, an increased incidence of thyroid follicular cell hypertrophy in both sexes, and altered colloid in males. These effects are considered an adaptive response and not adverse.
870.3100 / 90-day Oral/ rat	M: 0, 3.2, 9.3, 228 F: 0, 3.7, 11.4, 260	228(male) and 260 (female)	Not identified	Increased liver weights and an increased incidence of centrilobular hepatocellular hypertrophy were observed, which were not accompanied by alterations in relevant clinical chemistry parameters or adverse liver lesions. The effects observed are considered adaptive and not adverse over this time frame.
870.3100/ 90-day Oral/ mouse	M: 0, 26.9, 638, 1238 F: 0, 31.5, 757, 1600	1238 (male) and 1600 (female)	Not identified	Liver effects are considered adaptive and not adverse.
870.3150/ 90-day Oral/ Dog	M: 0, 5.6, 55.7, 532 F: 0, 6.1, 63.1, 568	55.7 (male) and 63.1 (female)	M = 532 F = 568	NOAEL based on the minimal liver effects (increased liver weight and hepatocellular hypertrophy), which were not accompanied by significant alterations in relevant clinical chemistry parameters or adverse liver lesions in both sexes. The effects observed are considered adaptive and not adverse over this time frame. LOAEL based on decreased body weight/body weight gain in females, increased alkaline phosphatase activity in both sexes, increased GGT activity in both sexes, decreased albumin in males, increased liver weights in both sexes, increased adrenal weights in males, increased incidence of hepatocellular hypertrophy in both sexes, and an increased incidence of slight diffuse cortical hypertrophy/hyperplasia in the adrenal in males.
870.3200/ 28-Day dermal toxicity/rat	0, 100, 300, 1000	1000	Not identified	Increased lymphocyte debris within the thymic cortex (♂/♀; 7/10 each); lesion characterized by the increased presence of fragmented thymic cortical lymphocytes noted within tingible body macrophages; finding not accompanied by a decrease in the size or weight of the thymus or changes in lymphocyte counts. The significance of the finding at the limit dose is not known.

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
870.3700a/ Prenatal development/ rat	0, 30, 100, 300 GD6-20	Maternal = 300 Develop = 300	Not identified	Maternal: Findings at the 300 mg/kg/day dose level are considered minimal. The dose levels do not appear adequate for assessing the developmental toxicity potential of BYF 14182. Although there was a significant reduction in maternal body weight gain at 300 mg/kg/day, which correlated with a decrease in food consumption, body weights were comparable to those of the control, and the liver changes are considered adaptive and not adverse. Developmental toxicity NOAEL: At 300 mg/kg/day, the highest dose tested, no adverse effects were observed. However, this dose was a no adverse effect dose level in the range-finding study also. The dose levels are not considered adequate for assessing the developmental toxicity potential of BYF 14182. Little concern that new studies would identify a developmental endpoint with a NOAEL lower than the NOAELs selected for risk assessment.
870.3700b/ Prenatal development/ rabbit	0, 30, 100, 600 GD6-28	Maternal = 600 Develop = 600	Not identified	The maternal findings at the 600 mg/kg bw/day dose level are considered minimal. The dose levels do not appear adequate for assessing the developmental toxicity potential of BYF 14182 in the rabbit. Although there was a significant reduction in maternal body weight gain at 600 mg/kg/day, which correlated with a decrease in food consumption, body weights were comparable to those of the control. No other effects were observed. Developmental findings: Little concern that new studies would identify a developmental endpoint with a NOAEL lower than the NOAELs selected for risk assessment.
870.3800/ Repro & fertility effects/ rat	M: 0, 12.8, 64.1, 252.2 F: 0, 15, 75.9, 294.5	Parental/ Systemic: 64 (male) and 76 (female) Repro: 73 Offspring: 73	Parental/ Systemic: 252.2 (male) and 294.5 (female) Repro: 291 Offspring: 291	**Parental/Systemic: B**based on decreased body weight, decreased body weight gain, alterations in food consumption, decreased thymus weight in both genders, and decreased spleen weights in females (both generations). The increased liver weights and hepatocellular hypertrophy are considered adaptive and not adverse. **Reproductive** : Based on delayed sexual maturation in females in both generations.

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
				Offspring: Based on a slight decrease in litter size in both generations, decreased pup body weight and pup body-weight gain, delayed vaginal patency in both generations, and decreased brain, spleen, and thymus weights.
870.4100a/ Chronic toxicity/rat	M: 0, 4.0, 79, 288 F: 0, 5.6, 113, 399	2000 ppm (79/113)	7000 ppm (288/399)	Based on decreased body weight/body weight gain in females, increased liver weight in both sexes, increased incidence of centrilobular to panlobular hepatocellular hypertrophy and centrilobular hepatocellular macrovacuolation in both sexes, increased incidence of hepatocellular brown pigment in females, hepatocellular necrosis, colloid alteration in the thyroid in females, and increased cholesterol in females. These effects are considered mainly adaptive in nature.
870.4100b/ Chronic toxicity/dog	M: 0, 6.8, 32.0, 357 F: 0, 7.7, 37.9, 425	32	357	NOAEL is based on the minimal changes in the liver (increased liver weight and hepatocellular hypertrophy, which were not accompanied by relevant changes in clinical chemistry parameters and adverse liver lesions) that are not considered adverse. LOAEL is based on decreased body weight and body weight gain in females, increased prothrombin time in males, increased alkaline phosphatase activity in both sexes, increased GGT levels in both sexes, increased liver weights in both sexes, increased hepatocellular hypertrophy in both sexes, and an increased incidence of thyroid follicular cell hypertrophy in both sexes.
870.4200/ Carcinogen/ rat	M: 0, 4.0, 79, 288 F: 0, 5.6, 113, 399	See above under chronic toxicity rat	See above under chronic toxicity rat	There are three tumor types (brain astrocytomas in males, ovarian tubulostromal neoplasms in females, and histiocytic sarcoma in males). Penflufen was evaluated by the EPA HED Cancer Assessment Review Committee (CARC) on February 16, 2011, and it was concluded that penflufen should be classified Suggestive, quantification not required. All 3 tumor types were considered treatment-related. Dosing was considered adequate based on the presence of tumors.
870.4300/ Carcinogen/ mouse	M: 0, 14.3, 146, 880 F: 0, 18.4, 182, 1101	6000 ppm (880/1101)	Not identified	LOAEL: included a dose level that exceeded the limit dose in females and one that was close to the limit dose in males. The liver effects and associated effects on the thyroid are considered adaptive and not adverse. **no evidence of carcinogenicity**
870.5100/ Ames assay Salmonella	16 to 5000 µg BYF 14182			Negative with and without metabolic activation

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
typhimurium TA98, TA100, TA1535, Ta1537, Ta1538				
870.5100/ Ames assay Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	3 to 5000 µg BYF 14182			Negative with and without metabolic activation
870.5100/ Ames assay Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	16 to 5000 µg			Negative with and without metabolic activation
870.5100/ Ames assay Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	16 to 5000 µg BYF 14182-pyrazolyl-AAP			Negative with and without metabolic activation
870.5300/ *In vitro* V79/HPRT test – forward mutation (BYF 14182)	Experiment 1: without S9: 0, 25, 50, 75, 100, 125, 150 or 175 µg/mL; with S9: 0, 50, 75, 100, 125, 150, 175 or 200 µg/mL Experiment 2: without S9: 0, 12.5, 25, 50, 75, 100 or 125 µg/mL; with S9: 0, 25, 50, 75, 100, 125 or 150 µg/mL			Negative with and without metabolic activation
870.5300/ *In vitro* V79/HPRT	E1&E2: without S9: 0, 4.5, 9, 18, 27, or 36 µg/mL			Negative with and without metabolic activation

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
test – forward mutation (BYF 14182)	E1:with S9: 0, 4.7, 9.4, 18.8, 37.5, or 75 µg/mL E2: with S9: 0, 18.8, 37.5, 75, 100, or 125 µg/mL			
870.5300/ *In vitro* V79/HPRT test – forward mutation (BYF 14182-3- hydroxy-butyl)	0, 75, 150, 300, 600, 900, or 1200 µg/mL (+/-S9)			Negative with and without metabolic activation
870.5300/ *In vitro* V79/HPRT test – forward mutation (BYF 14182-3- pyrazolyl-AAP)	0, 3, 6, 12, 24, 36, 48, or 60 µg/mL (+/-S9)			Negative with and without metabolic activation
870.5375/ Chinese Hamster V79 cells – chromosome aberrations (BYF 14182)	4-hour: 0, 10, 20, 40, 70, and 100 µg/mL (-S9) 18-hour: 0, 3, 6, 12, 24, 36 µg/mL (-S9) 4-hour: 0, 15, 30, 60 and 90 µg/mL (+ S9) 4-hour: 0, 40, 70, and 100 µg/mL (-S9) and 0, 60, 75, and 90 µg/mL (+S9) (harvested 30 hours after treatment)			Negative with and without metabolic activation
870.5375/ Chinese Hamster V79 cells – chromosome aberrations (BYF 14182)	-S9: 0, 9.4, 18.8 and 37.5 □g/mL (4-hour treatment) –S9: 0, 4.7, 9.4 and 18.8 µg/mL (18-hour treatment) +S9: 0, 18.8, 37.5 and 75.0 µg/mL (4-hour treatment)			Negative with and without metabolic activation

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
	+S9: 0, 100, 150 and 300 µg/mL were harvested at 28 hours cytotoxicity determination 4.7-1200 µg/mL (±S9) 2.3-300 µg/mL (±S9).			
870.5375/ Chinese Hamster V79 cells – chromosome aberrations (BYF 14182-3-hydroxy-butyl)	-S9: 0, 150, 300, 600, 900, and 1200 µg/mL (4-hour treatment), and 0, 75, 150, 300, 450, and 600 µg/mL (18-hour treatment) +S9: 0, 75, 150, 300, 600, and 900 µg/mL (4-hour treatment); harvested 18 hours after treatment. 600, 900, and 1200 µg/mL (-S9) and 300, 600, and 900 µg/mL (+S9); harvested 30 hours after treatment (4-hour treatment).			Negative with and without metabolic activation
870.5375/ Chinese Hamster V79 cells – chromosome aberrations (BYF 14182-pyrazolyl-AAP)	-S9: 0, 15, 30 and 60 µg/mL (4-hour and 18-hour treatments) +S9: 0, 15, 30 and 60 µg/mL (18-hour harvest after treatment)			Negative with and without metabolic activation
870.5375/ Mouse Micronucleus	250, 500, 1000 mg/kg (male)			Negative
870.6200a/ Acute neurotoxicity screening battery	0, 100, 500, or2000	50	100	LOAEL: Based on decreased motor activity and locomotor activity in females
870.6200b/ Subchronic neurotoxicity		2000 ppm (126/156)	8000 ppm (516/609)	based on a slight decrease in motor activity in females, which is consistent with a similar finding of decreased motor activity in females

Table 4. Subchronic, Chronic and Other Toxicity Profile

Guideline/ STUDY/ SPECIES/	DOSES (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	EFFECTS
screening battery				in the acute neurotoxicity study.
870.7485/ Metabolism & pharmaco –kinetics (species)				**Single dose:** elimination pharmacokinetics; rapid absorption & elimination; no apparent effect of increasing dose on absorption or elimination, although differences between sexes in amount in feces/urine. **Metabolism, single dose:** most excreted in feces (males)/urine (females); widely distributed with highest concentration in liver and kidneys; biotransformation characterized as very fast; complex mixture of metabolites. **Metabolic pathway, single dose:** 94-97% excreted; numerous metabolites identified; almost complete absorption **Multiple dosing:** not performed
870.7600/ Dermal penetration/ rat (male)	1, 50, or 240 g/L for 8 hours (achieved doses ranged from 0.010 to 0.011 mg/cm^2, 0.50 to 0.53 mg/cm^2, and 2.63 to 2.73 mg/cm^2)			maximum % absorbed was 1.442%, 4.152%, and 5.350% for high, mid, and low dose formulations, respectively
OECD 428/ *In vitro* dermal absorption/ human & rat	Doses: 50 g/L, 10 g/L, and 1 g/L			mean total amounts of [^{14}C] considered to be potentially absorbable (*directly absorbed + total remaining at dose site*) at doses of 50 g/L, 10 g/L, and 1 g/L were 4.115%, 5.754%, and 6.516%, respectively, for rat skin and 0.172%, 1.449%, and 1.457%, respectively, for human skin; mean % of the applied dose potentially absorbable was 24-fold, 4-fold, and 4.5-fold greater in the rat skin than in the human skin, respectively.
870.7800/ Immuno-toxicity/ mouse	M: 0, 17.9, 82.6, 755.6 F: 0, 20.4, 104.5, 960.5	755.6(male) and 960.5 (female)	Not established	

Food Quality Protection Act (FQPA) Decisions:

The Agency concluded that the toxicology database is adequate for Food Quality Protection Act (FQPA) purposes and that there are no concerns or residual uncertainties for pre-/post-natal toxicity. Therefore, a FQPA factor of 1X was selected. That decision was based on the following findings:

a. The toxicology database for penflufen is complete and includes acceptable developmental toxicity studies in rats and rabbits, a two generation reproductive toxicity study in rats, acute and subchronic neurotoxicity

screening studies in rats, and an immunotoxicity study.

b. Although there is some evidence of qualitative sensitivity of the young (delayed sexual maturation and decreased litter size), the effects are well characterized, and there is a clear NOAEL. The dose level where offspring effects were identified in the reproduction study is comparable to the high dose used in the rat developmental toxicity study where no effects were identified in either the maternal or fetal rat. Since minimal/no effects were observed in the developmental toxicity studies following exposure of the maternal animals to dose levels equal to and greater than those tested in the studies used for risk assessment, there is little concern that new studies would identify a developmental endpoint with a NOAEL lower than the NOAELs selected for risk assessment.

c. Although decreased motor activity was observed following acute oral exposure, no neuropathological lesions were observed and there is little concern for neurotoxicity. There is no indication that penflufen is a neurotoxic chemical and there is no need for a developmental neurotoxicity study or additional uncertainty factors (UFs) to account for neurotoxicity.

d. There is no residual uncertainty in the exposure database for penflufen with respect to dietary (food and water) exposure.

   A complete database with respect to both the nature and magnitude of residues expected in food has been provided. The dietary food exposure assessment is based on tolerance level residues, assumes 100% crop treated for all commodities, and incorporates processing factors as appropriate which results in very high-end estimates of dietary food exposure. Further, highly conservative, modeled drinking estimates of exposure were included in the assessments. Actual exposures and risks from penflufen in food and drinking water are likely to be far lower than estimated in this risk assessment.

Dietary Exposure and Risk:

The acute and chronic dietary risk assessments utilized the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Highly conservative acute and chronic dietary assessments were conducted using tolerance level residues, 100% crop treated assumptions, default DEEM processing factors for dried potatoes and modeled water numbers. Acute and chronic dietary risks to all populations were <1% of the aPAD and cPAD, respectively. These assessments are considered to be highly conservative and unlikely to underestimate acute or chronic dietary (food and water) exposures and risks.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure, mg/kg/day	% aPAD	Exposure, mg/kg/day	% cPAD
U.S. Population	0.000949	<1	0.000407	<1
All infants (<1 yr)	0.003364	<1	0.001231	<1
Children 1-2 yrs	0.001546	**<1**	0.000650	**<1**
Children 3-5 yrs	0.001404	<1	0.000613	<1
Children 6-12 yrs	0.000975	<1	0.000424	<1
Youth 13-19 yrs	0.000777	<1	0.000312	<1
Adults 20-49 yrs	0.000857	<1	0.000373	<1
Adults 50+ yrs	0.000773	<1	0.000381	<1
Females 13-49 yrs	0.000856	<1	0.000369	<1

Residential Exposure Estimates:

Residential exposures and risk were not assessed because the proposed uses of penflufen do not involve applications by homeowners or commercial applicators in residential settings at this time and there are no existing or proposed residential uses.

Aggregate Risk:

There are no residential uses for penflufen; therefore the aggregate exposure and risk assessments include acute and chronic dietary (food and water) only. There are no aggregate risk estimates of concern for the proposed new uses of penflufen

Occupational Exposure:

Occupational Handler exposure is expected for individuals involved in commercial seed treatment (primary handlers) and planting treated seeds (secondary handlers). Quantification of dermal exposure and risk is not required since a dermal hazard has not been identified for penflufen. Only inhalation exposure and risks were quantified. The inhalation Margins of Exposures for occupational handlers ranged from 15,000 to 14,000,000. All inhalation risk estimates have MOEs greater than 100 and therefore, are not of concern.

The potential for occupational dermal exposure to penflufen during post-application activities is unlikely because sustained levels of contact with treated seed is not expected after the seed has been placed in the soil or other planting media. Also, as no dermal hazard has been identified, no quantitative post-application assessment is required for exposure to treated seeds that have already been planted. A postapplication inhalation exposure assessment is not required as exposure is expected to be negligible.

5. ENVIRONMENTAL EXPOSURE AND RISK

Environmental Characteristics:

Penflufen is persistent in aerobic and anaerobic conditions, and is moderately mobile based on the FAO Soil mobility classifications (mean Koc = 365). Penflufen is persistent in soil with half-lives ranging from 115 to 433 days in aerobic soil. It degrades very slowly in anaerobic soil with an extrapolated half-life of 886 days. There is no evidence of degradation via hydrolysis, which was studied across environmental pHs (pH 5, 7, and 9). Penflufen degraded slowly by aerobic aquatic metabolism with half-lives ranging from 267 to 301 days and there is no evidence of degradation in anaerobic aquatic systems. The primary route of degradation is via aqueous photolysis, however, photolysis only plays a significant role in shallow clear waters. Penflufen does not bioconcentrate in aquatic organisms. Penflufen is locosystemic and is not transported acropetally in foliage as the plants emerge and grow. The greatest exposure is expected from animals directly ingesting treated seed.

Penflufen and its residues of concern (Pen-3HB, and AAP) are expected to persist in both the terrestrial and aquatic environments. Pen-3HB is much more mobile than the parent, but the AAP degradate is comparatively immobile. Under aerobic conditions, the compound can be slowly metabolized, but it is stable to anaerobic metabolism. AAP will persist with half-lives ranging from 116-260 days (there is no metabolism data for the Pen-3HB degradate). Penflufen was detected in the submitted terrestrial field dissipation studies above the level of quantitation (LOQ) up to 60cm depth, however the majority of the detections were only reported in the upper soil layers (0-15 cm).

Eco-toxicity data are available for PEN-3HB and AAP indicating that these two degradates are no more, and often less, toxic compared to the technical based on the most sensitive taxa tested. Aquatic and terrestrial exposure estimates were based on the residue levels of the parent compound alone.

Table 6. Laboratory Environmental Fate Data for Penflufen

Data	Units	Value
Molecular Weight	g/mol	317.41
Water Solubility (20ºC, pH 7)	mg/L	10.9
Vapor Pressure (25ºC)	Torr	9.0×10^{-9}
Henry's law Constant	atm m^3/mol	1.04×10^{-10}
Hydrolysis $t_{1/2}$ at 50 ºC	Days	Stable
Photodegradation in Water	Days	83.2
Aerobic Soil Metabolism $t_{1/2}$ at 25°C (combined radio-label half-life)	Days	249 (silt loam) 433 (sandy loam)
Aerobic Soil Metabolism $t_{1/2}$ at 20°C	Days	117 (silt loam) 164 (sandy loam)* 243 (loam)* 129 (loam)* AAP degradate: 257 (sandy loam)* 116 (silt loam) 231 (loam)*

		128 (clay loam)*
Anaerobic Soil Metabolism $t_{1/2}$ at 20°C	Days	866*
Aerobic Aquatic Metabolism $t_{1/2}$ at 20°C (sandy loam:sediment system, 2 radio-labels)	Days	301* 267*
Anaerobic Aquatic Metabolism $t_{1/2}$ at 20°C (combined labels)		Stable – no evidence of degradation

*extrapolated beyond the study duration

Ecological Effects and Risk:

Terrestrial Hazard

Birds-

Studies of acute oral (dose based) toxicity to bobwhite quail and canary indicated that penflufen is practically nontoxic when administered as a single oral dose. Since the LD_{50} and LC_{50} values exceeded the highest treatment levels tested in the submitted acute oral and sub-acute dietary avian studies, the standard RQs for acute and sub-acute exposure were not calculated. Two subacute dietary toxicity studies indicated that technical penflufen is practically nontoxic to the mallard duck and bobwhite quail. In the chronic studies conducted with technical penflufen no effects were observed in the bobwhite quail study. However, at all concentrations tested with the technical, treatment related effects were noted on the number of eggs hatched per live embryo in the mallard duck reproduction toxicity. Chronic RQs were derived as a screening exercise in the Risk Estimation for the non-definitive risk measure of effects to birds (NOAEC <292 mg ai/kg-diet). As a minimum level of risk, none of the RQs for any proposed uses of penflufen exceeded the Agency's chronic risk to birds LOC of 1.0. The highest RQ-value (0.49) is for the proposed canola and sunflower uses.

Mammals-

Acute toxicity study effects for the technical active ingredient in mammals are reported as follows:

Acute Oral Toxicity LD50: >5000 mg/kg (Rat)
Acute Dermal Toxicity LD50: >2000 mg/kg (Rat)
Acute Inhalation Toxicity LC50: >2.02 mg/L (Rat)

The chronic mammalian RQs for all applications of penflufen fell below the Agency's risk to listed and nonlisted mammalian species LOC of 1.0, with a calculated maximum RQ of 0.14 for the proposed canola and sunflower uses.

Additional product mixtures were tested: penflufen plus prothioconazole plus metalaxyl, penflufen plus prothioconazole, penflufen plus trifloxystrobin, and penflufen plus clothianidin. While none were an actual final product formulation, they represented a suite of "typical" coformulants, each in relative amounts found in products, mixed in

water and administered by gavage. Each study resulted in an LD_{50}> 2000 mg mixture/kg bw.

No reproduction toxicity was observed in a two-generation reproduction study with penflufen in rats. There was one set of litters per generation. The parental systemic LOAEL was 4000 ppm based on decreased body weight, decreased body weight gain (both generations). The parental systemic NOAEL is 1000 ppm. The offspring LOAEL is 4000 ppm based on a slight decrease in litter size in both generations, decreased pup body weight and pup body-weight gain. The offspring NOAEL is 1000 ppm. There was no treatment-related effect on reproductive performance in either the P or the F_1 generation. The reproductive NOAEL is 4000 ppm, the highest dose tested.

Invertebrates-

Results of available toxicity studies indicate that direct contact and oral exposure to penflufen is not likely to adversely affect honey bee pollinators (young adult forage bees) (*Apis mellifera*), though there are effects on the fecundity of *Aphidius rhopalosiphi*, a parasitoid wasp, and earthworms (*Eisenia foetida*) on an acute contact exposure basis. It is not clear from the available data whether there would be effects on larval bee pollinators or what the route of exposure would be. There is no evidence at this time of effects on larval bees and there is no vetted risk assessment process for this route of exposure for these taxa. There have been advances in pollinator study designs which were discussed at the Pellston Conference supported by the Society of Environmental Toxicology and Chemistry (SETAC). The Agency is in the process of developing a risk assessment process for pollinators in conjunction with the results of the SETAC Pellston Conference. Ultimately this will be reviewed by the Scientific Advisory Panel. Based on the available data, precautionary label language for bees does not appear necessary for end-use products with penflufen as the only active ingredient.

Aquatic Hazard

Freshwater and estuarine/marine fish-

Results of acute toxicity studies in freshwater and estuarine/marine fish indicate that penflufen is highly to very highly toxic to fish on an acute exposure basis. Dose-dependent sublethal effects observed in fish studies included surfacing, lethargy, erratic swimming, loss of equilibrium, loss of vertical orientation, labored respiration, and lying on the bottom. Reduced fish length was observed in the F1 generation of the available ELS study. Quiescence, pale color and abnormal positioning were reported sublethal effects in invertebrates. Penflufen is classified as moderately toxic to Eastern oysters and mysids on an acute exposure basis, however, using the observed NOAECs (440 and 1440 ug ai/L, respectively), the highest RQ-value would be 0.01. Most RQs for proposed uses of penflufen fall below the Agency's acute risk to listed species LOC (0.05), as well as the Agency's acute risk to non-listed species LOC of 0.5. The RQ from the proposed rice is equal to the listed species LOC. No other scenarios exceed the LOCs.

The RQs for chronic exposures also fell below the Agency's chronic risk to listed and non-listed species LOC (1.0).

A flow-through bioconcentration study of bluegill sunfish exposed to penflufen for 28 days indicated that the accumulation in fish does not exceed levels of concern. The bioconcentration factors (BCF) in low dose samples (0.45 µg/L) were 35, 186, and 100x for whole fish, edible, and non-edible fish tissues, respectively. In high dose samples (4.5 µg/L) the BCF's were 37, 187, and 103 for whole fish, edible, and non-edible fish tissues, respectively. BCF values less than 1000 do not trigger criteria for further evaluation of bioaccumulative compounds

Plants

Terrestrial Plants-

Tier I limit studies of the effect of the formulation PEN 240FS on seedling emergence and vegetative vigor in terrestrial plants indicated that terrestrial plants are relatively insensitive to penflufen at application rates slightly less than the maximum per acre application rate for the proposed registration uses.

Limit tests for both vegetative vigor and seedling emergence were conducted at the rate of 0.22 lbs ai/A. No effects >25% were observed in either study. Minimal measured inhibitions were observed in biomass and shoot length, and up to 5% in vegetative vigor study but none were statistically significant. In the seedling emergence study measured inhibition of 14% emergence was observed in onion and 10% and 12% biomass in buckwheat and soybean respectively but none were statistically significant.

Aquatic Plants-

Based on the available information on Lemna gibba and Pseudokirchneriella subcapitata, the proposed uses of penflufen do not exceed the LOC for aquatic plant (1.0) for either nonlisted or listed plants. The lowest NOAEC among the vascular and nonvascular studies involving the technical or a formulation was 520 µg ai/L for green algae (based on biomass and cell density). At that concentration the RQ = 0.006, whereas the LOC is 1.0. Therefore, potential risk to aquatic plants from the proposed uses of penflufen is expected to be low.

6. REGULATORY POSITION AND RATIONALE

Available data provide adequate information to support the unconditional registration of penflufen technical and end-use products on in-furrow potato use and seed piece treatment on vegetable, tuberous and corm, (CSG1C); for use as seed treatment fungicide on alfalfa; vegetable, legume (CG 6 & 7); grain, cereal (CG15 & 16); oilseed (CG 20).

Labeling Restrictions:

In order to mitigate potential risks to non-target organisms, such as non listed and listed birds and mammals, and to reduce risk of exposure in aquatic bodies, ground and surface water advisory statements along with directions for spilled seeds will be added on product labels and seed bag tags.

Environmental Hazards:

“This pesticide is toxic to fish.”

"Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwater or rinsate.”

“Runoff may be hazardous to aquatic organisms in water adjacent to treated areas."

“Treated seed exposed on soil surface may be hazardous to wildlife. Cover or collect seeds spilled during loading.”

Directions for Use – Precautions and Restrictions:

“For commercial application only. For use only in commercial seed treatment equipment. Not for use in hopper-box, slurry-box, or other on-farm seed treatment applicators.”

“Apply using commercial slurry or mist-type seed treatment equipment.”

If the product does not have colorant then the label should have the following for the commercial application portion of the label: “All seed must be adequately dyed with a suitable colorant to prevent its accidental use as food for man or feed for animals. Refer to 21CRF, part 2.25. Any colorant added to treated seed must be cleared for use under 40CFR, Part 153.155.”

Treated seed must be labeled in accordance with the requirements of the Federal Seed Act. In addition, the US EPA requires the following statements on the Seed Bag Tag attached to the container of seed treated with penflufen:

Required Labeling for Seed Bag Tags:

“Do not use treated seed for food, feed, or oil production. Excess treated seed may be used for ethanol production only if (1) by-products are not used for livestock feed and (2) no measurable residues of pesticides remain in ethanol by-products that are used in agronomic practice.”

“Store away from feeds and other foodstuffs”

“Wear long sleeved shirt, long pants, and chemical resistant gloves when handling treated seed.”

“Dispose of seed packaging in accordance with local requirements.”

“Do not re-use bags from treated seed to handle food or feed products.”

"Dispose of all excess treated seed. Left over treated seed may be double sown around the headland or buried away from water sources in accordance with local requirements. Do not contaminate water bodies when disposing of planting equipment washwaters."

"Use planting equipment that will plant treated seed into the soil to a minimum depth of 0.5 inch."

"This compound is toxic to birds and mammals. Treated seed exposed on soil surface may be hazardous to birds and mammals. Cover or collect seeds spilled during loading."

8. CONTACT PERSON AT EPA

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DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only may not be used to fulfill data requirements for pesticide registration and reregistration. The information is believed to be accurate as of the date on the document.

APPENDIX I

GLOSSARY OF TERMS AND ABBREVIATIONS

ADNT	Acute delayed neurotoxicity
a.i.	Active Ingredient
aPAD	Acute Population Adjusted Dose
ARI	Aggregate Risk Index
BCF	Bioconcentration Factor
CAS	Chemical Abstracts Service
ChE	Cholinesterase
ChEI	Cholinesterase inhibition

cPAD	Chronic Population Adjusted Dose
%CT	Percent crop treated
DAT	Days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model - Food Consumption Intake Database
DNA	Deoxyribonucleic acid
DNT	Developmental neurotoxicity
DIT	Developmental immunotoxicity
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
GLC	Gas Liquid Chromatography
GLN	Guideline Number
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOAEL	Lowest Observed Adverse Effect Level
LOAEC	Lowest Observed Adverse Effect Concentration
LOC	Level of Concern
LOD	Limit of Detection
LOQ	Limit of Quantitation
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number), EPA's system of recording and tracking studies submitted
MTD	Maximum tolerated dose
NA	Not Applicable
NOEC	No Observable Effect Concentration
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
NOAEC	No Observed Adverse Effect Concentration
NPDES	National Pollutant Discharge Elimination System
OP	Organophosphate
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PAG	Pesticide Assessment Guideline
PAM	Pesticide Analytical Method

PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
RAC	Raw Agriculture Commodity
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
TGAI	Technical Grade Active Ingredient
UF	Uncertainty Factor
µg	micrograms
µg/L	Micrograms Per Liter
µL/g	Microliter per gram
USDA	United States Department of Agriculture
WPS	Worker Protection Standard

APPENDIX II

Citations Considered to be Part of the Data Base Supporting the Registration of Penflufen.

48023544 Fent, G. 2007. [Pyrazole-3-^{14}C]BYF14182-3-hydroxy-butyl (BCS-AA10006): Adsorption/desorption in five different soils. Unpublished study performed by RLP AgroScience GmbH, Weinstrabe,.

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48023546 Heinemann, O. and D. Dehner. 2006. [Phenyl-UL-$^{13}C_6$/^{14}C]BYF14182: Adsorption/desorption on five soils. Study No. M1311493-2. Unpublished study performed and sponsored by Bayer CropScience AG, Monheim am Rhein, Germany

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