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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: 11-15-11

SUBJECT: **Penflufen.** New Active Ingredient-New Uses on Alfalfa, Potato (Crop Subgroup 1C), Legume Vegetables (Crop Group 6 and Crop Group 7), Cereal Grains (Crop Group 15 and Crop Group 16), and Oilseeds (Crop Group 20). Residue Chemistry Summary Document. Australian/Canadian/U.S. Joint Review.

PC Code: 100249
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Petition No.: PP# 0F7711

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TXR No.: NA
MRID No.: See Table Below

DP Barcode: D395192
Registration No.: 264-RRRI, 264-RRRO, 264-RREN, 264-RREL, 264-RREU, 264-RRER, 263-RREE, 264-RREG
Regulatory Action: New Active Ingredient; Section 3 Registration
Case No.: NA
CAS No.: 494793-67-8
40 CFR: TBD

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Attached please find the residue chemistry summary document for the new fungicide, penflufen. This assessment addresses the active ingredient, penflufen only, with one exception. In reviewing end use product labels, rotational crop language recommendations are based on consideration of all active ingredients in the formulation. All other residue chemistry considerations for co-formulants will be addressed in separate residue chemistry summary documents as appropriate.

Rec'd RRC 11/23/11

MRID Summary Table		
Study Type	**MRID**	**Comments**
Waiver-livestock feeding study	48023723	Separate DER not required.
Magnitude of the residue in/on wheat	48023724	DER in Appendix 3
Magnitude of residues in/on barley	48023725	DER in Appendix 3
Magnitude of the residue in/on corn	48023726	DER in Appendix 3
Magnitude of the residue in/on legume vegetables	48023727	DER in Appendix 3
Magnitude of residues in/on soybean	48023728	DER in Appendix 3
Magnitude of the residue in/on potatoes	48023729	DER in Appendix 3
Magnitude of residues in/on corn (5X)	48023734	DER in Appendix 3
Magnitude of residues in/on wheat (5X)	48023735	DER in Appendix 3
Magnitude of residues in/on soybean (5x)	48023736	DER in Appendix 3
Potato processing study	48023737	DER in Appendix 3
Magnitude of the residue in field rotational crops	48023741	DER in Appendix 3
Magnitude of the residue in field rotational crops	48023743	DER in Appendix 3
Proposed tolerance summary	48023917	Separate DER not required.
Metabolism in potatoes	48023634	DER in Appendix 1
Metabolism in potatoes	48023635	DER in Appendix 1
Metabolism in spring wheat	48023636	DER in Appendix 1
Metabolism in spring wheat	48023637	DER in Appendix 1
Metabolism in soybeans	48023638	DER in Appendix 1
Metabolism in soybeans	48023639	DER in Appendix 1
Metabolism in paddy rice	48023640	DER in Appendix 1
Metabolism in paddy rice	48023641	DER in Appendix 1
Determination of TRR in sunflower	48023642	DER in Appendix 3
Determination of TRR in corn	48023643	DER in Appendix 3
Determination of TRR in cotton	48023644	DER in Appendix 3
Determination of TRR in canola	48023645	DER in Appendix 3
Determination of TRR in legumes	48023646	DER in Appendix 3
Determination of TRR in peas	48023647	DER in Appendix 3
Determination of TRR in alfalfa	48023648	DER in Appendix 3
Metabolism in the laying hen	48023649	DER in Appendix 1
Metabolism in the laying hen	48023650	DER in Appendix 1
Metabolism in the lactating goat	48023701	DER in Appendix 1
Metabolism in the lactating goat	48023702	DER in Appendix 1
Analytical method	48023703	DER in Appendix 2
Analytical method	48023704	DER in Appendix 2
Multi-residue Method	48023705	DER in Appendix 2
Independent laboratory validation	48023706	DER in Appendix 2
Analytical method	48023707	DER in Appendix 2
Analytical method	48023708	DER in Appendix 2
Independent laboratory validation	48023709	DER in Appendix 2
FDA PAM Multiresidue method (MRM) testing	48023710	DER in Appendix 2
Analytical Method	48023711	DER in Appendix 2
Storage stability	48023720	DER in Appendix 1
Interim Storage stability	48023721	DER in Appendix 1
Metabolism in confined rotational crops	48023738	DER in Appendix 1
Metabolism in confined rotational crops	48023739	DER in Appendix 1
Determination of TRR in confined rotational crops	48023740	DER in Appendix 1
Final Storage Stability Study	48516101	DER in Appendix 4

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1.0 Executive Summary

Penflufen is a new carboxamide fungicide proposed for use as a seed treatment in alfalfa, potatoes (tuberous and corm crop subgroup 1C), legume vegetables (crop group 6 and crop group 7), cereal grains (crop group 15 and crop group 16), and oilseeds (crop group 20). An in-furrow application to potatoes is also proposed. The reported pesticidal mode of action is as an inhibitor of mitochondrial respiration by inhibiting succinate dehyrogenase, an enzyme in the electron transport system. Bayer CropScience has requested registration of the uses listed above and the establishment of tolerances to support those uses. Penflufen is being reviewed as part of a global work-sharing project with the regulatory authorities in Australia (APVMA) and Canada (PMRA).

There are seven end use products associated with this petition. All end-use products are liquid concentrate formulations which contain 0.32-2.0 lb active ingredient (ai)/gal. The formulations differ by their inclusions of various co-formulants or a dye. Penflufen is proposed for use as a seed treatment at rates from 0.002–0.015 lb ai/100 lb seed applied as a slurry or mist-type seed treatment. An in-furrow application is permitted at ~0.2 lbs ai/A using ground spray equipment.

The nature of the residue in plants is adequately understood for the purpose of the proposed seed treatment and potato in-furrow uses only. Plant metabolism data were submitted for potato (seed treatment and in-furrow applications), wheat (seed treatment), soybean (seed treatment), and rice (at transplant). The submitted data on the metabolism of penflufen demonstrate that residues are generally low, but do translocate throughout the plants. The highest residues are generally found in the foliage or forage portions of plants (feedstuffs), and not in the tubers, seeds or grains of these commodities (food items). The metabolic pathway in potatoes, wheat, soybeans and rice is substantially similar and the residue of concern in plants for both tolerance setting and risk assessment purposes is the parent compound only. While the proposed metabolic pathways for these crops are similar, in the absence of data on a fruiting vegetable, this data set is not considered adequate to define the nature of the residue in all plants. Further, since the application techniques were limited to seed treatment, in-furrow or at transplant (rice), these data will not support foliar uses of penflufen on agricultural crops.

Confined rotational crop studies show that the metabolic pathway in rotational crops appears to be substantially similar to the metabolism in primary crops. The residue of concern for tolerance setting and risk assessment purposes in rotational crops is the parent compound, penflufen.

The registrant has submitted ruminant and poultry metabolism studies. Penflufen is extensively metabolized in the hen and lactating goat. The metabolic pathways in poultry and ruminants appear similar. The submitted livestock metabolism studies adequately address the requirement to elucidate the nature of the residue in livestock for penflufen. However, a final determination on the residues of concern in livestock has not been made since the Agency has determined that the newly proposed uses of penflufen are classified as 180.6 (a) (3), no reasonable expectation of finite residues with respect to residues in livestock commodities since quantifiable residues are not likely to be present in the livestock feedstuffs associated with this petition.

Analytical methods used to generate the residue data submitted in support of this petition have been adequately validated. Additionally, an adequate analytical method is available to enforce

the proposed tolerances for penflufen in plant commodities. The LC/MS/MS (liquid chromatography with tandem mass spectrometry) method, EL-002-P09-03, has been adequately validated, has undergone a successful ILV (independent laboratory validation), is considered adequately radiovalidated and has been reviewed by the Agency for appropriateness as an enforcement method. Penflufen is not recovered by any FDA multi-residue protocol.

Adequate storage stability data have been provided to support the intervals of frozen storage for all the studies in the residue chemistry database. Residues of penflufen are stable for up to 27 months when stored frozen.

In lieu of field trial data, Bayer CropScience has provided total radioactive residue (TRR) studies on alfalfa, sunflower, cotton and canola that demonstrate there is no uptake of radioactivity into any aerial portion of those plants. The uses on alfalfa, sunflower, cotton and canola meet the requirements for a non-food use classification. However, the registrant has requested tolerances for these commodities in the interest of international harmonization. Field trial data submitted for the remaining commodities showed no quantifiable residues of penflufen in any of the food or feedstuffs associated with the remainder of the commodities that are the subject of this petition.

The uses on alfalfa, sunflower, cotton and canola are considered to be non food uses. However, the registrant has requested tolerances for these commodities in the interest of international harmonization.

A potato processing study and exaggerated rate field trials (5X proposed application rates) for soybean, wheat and corn were provided to address the fate or penflufen residues in processed commodities. The potato study indicated that residues of penflufen do not concentrate in potato processed commodities with the exception of wet potato peel. While residues in wet peel may concentrate up to ~4X, the processing study used samples from a 5X exaggerated rate field trial, and even with concentration, residues in wet peel are not expect to exceed the established tolerance for potatoes of 0.01 ppm; therefore a separate processed commodity tolerance is not required. Residues in soybean seed, wheat grain and corn grain were all <LOQ from 5X studies; therefore additional processing data is not required and the Agency concludes that quantifiable residues of penflufen are not likely in soybean, wheat or corn processed commodities.

Limited rotational crop field trial data were provided for penflufen. No residues of concern were identified in any of the rotational crops at a 30-day plant back interval (PBI); therefore, tolerances in rotational crops are not required to support the 30-day PBI on the submitted labels.

Since there are no quantifiable residues in the food and feedstuffs that are the subject of this petition, the supported tolerance level is at the analytical method limit of quantitation (LOQ) of 0.01 ppm. There are no Codex or Mexican MRLs for penflufen and U.S. and Canadian tolerances are fully harmonized; therefore, there are no issues with respect to international harmonization associated with the tolerances recommended in this action.

2.0 Regulatory Recommendations and Residue Chemistry Deficiencies

2.1 Data Deficiencies/Conditions of Registration

Provided the registrant revises the proposed labels for penflufen end use products as described in Section 2.3, below, there are no residue chemistry deficiencies that would preclude the requested registration of penflufen for use as a seed treatment in potatoes, legume vegetables, cereal grains, oils seeds and alfalfa or as an in-furrow application to potatoes. A human health risk assessment is forthcoming.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate analytical method is available to enforce the proposed tolerances for penflufen in plant commodities. The LC/MS/MS (liquid chromatography with tandem mass spectrometry) method, EL-002-P09-03, has been adequately validated, has undergone a successful ILV (independent laboratory validation), is considered adequately radiovalidated and has been reviewed by the Agency for appropriateness as an enforcement method.

Bayer method EL-002-P09-03 is described briefly as follows. Samples are homogenized and extracted with 4:1 acetonitrile/water repeatedly. The extracts are combined and taken to dryness. Hydrochloric acid is added to the dried extract and the solution is heated to hydrolyze any conjugates. The sample is then neutralized with sodium hydroxide, diluted with formic acid in water, and an isotopically labeled internal standard is added. Penflufen is quantitated by high performance liquid chromatography/triple stage quadrupole mass spectrometry (LC/MS/MS).

Penflufen has been subjected to analysis by the FDA multi-residue method protocols. Penflufen is not adequately recovered through any of the FDA multi-residue protocols.

2.2.2 International Harmonization

Penflufen is part of a global review project with Canada and Australia. During the course of the review, the Agencies reached agreement on both the tolerance expression for plant commodities and the tolerance levels for commodities common to the three countries. At this time no tolerances are required in the U.S. for livestock commodities; therefore, a discussion of international harmonization with respect to livestock commodities is not germane to this assessment.

There are no Codex or Mexican MRLs for penflufen and U.S. and Canadian tolerances are fully harmonized; therefore, there are no issues with respect to international harmonization associated with the tolerances recommended in this action.

2.2.3 Recommended Tolerances

Table 2.2.3 summarizes the registrant's proposed tolerances and the Agency's final tolerance recommendations. The tolerance expression for penflufen should read as follows:

> Tolerances are established for residues of the fungicide penflufen, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels for the penflufen is to be determined by measuring only penflufen (*N*-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide).

Table 2.2.3. Tolerance Summary for Penflufen

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments *Correct Commodity Definition*
Alfalfa, Forage	0.01	0.01	*Alfalfa, forage*
Alfalfa, Hay	0.01	0.01	*Alfalfa, hay*
Tuberous and Corm Vegetable (Crop Sub-group 1C)	0.01	0.01	*Vegetable, tuberous and corm, subgroup 1C*
Legume Vegetables, succulent or dried (Crop Group 6)	0.01	0.01	*Vegetable, legume, group 6*
Foliage of Legume Vegetables, including soybeans (Crop Group 7)	0.01	0.01	*Vegetable, foliage of legume, group 7*
Soybean, seed	0.01	-	Not required, soybean seed is included in crop group 6.
Cereal grains (Crop Group 15)	0.01	0.01	*Grain, cereal, group 15*
Forage, fodder and straw of Cereal grains (Crop Group 16)	0.01	0.01	*Grain, cereal, forage, fodder and straw, group 16*
Oilseeds (Crop Group 20)	0.01	0.01	*Oilseed, group 20*
Cotton, gin by-products	0.01	0.01	*Cotton, gin by-products*

2.2.4 Revisions to Petitioned-For Tolerances

The Agency is recommending that tolerances be set for the commodities requested by the registrant at the levels requested. However, minor modifications to some commodity definitions are recommended to be consistent with Agency naming-conventions for commodities.

2.3 Label Recommendations

HED is aware of the issue regarding the use of treated seeds (primarily corn) being used for ethanol production and the potential of pesticide residues occurring in the byproducts that can be used for livestock feed or fertilizer. The standard restriction with wording such as that on the proposed penflufen labels ("Do not use for feed, food or oil purposes") is not adequate to preclude this use of treated seeds. Since OPP is actively working with Bayer to develop a more appropriate label statement to address this concern, HED recommends that the wording to be developed

through this process be used on the labels of all the penflufen products.

Additional label-specific revisions are as follows. Note that the suggested rotational crop language includes consideration of rotational crop restrictions for penflufen as well as any co-formulant(s) in the end-use product.

PENPROME 177FS (264-RREE)

- The "rate per seed" for soybeans needs to be corrected to reflect the appropriate rate and AOSA (Association of Official Seed Analysts) recommendation of 4000 soybean seeds per pound.
- The crop rotation restriction should be revised to specify the following. "Crops for which there are registered use of penflufen, which includes alfalfa, potatoes (Crop Subgroup 1C), legume vegetables (Crop Group 6/7), cereal grains (Crop Group 15/16), and oil seeds (Crop Group 20) may be replanted at any time. All other crops may be planted no less than 30 days after planting treated seeds."

PEN 240FS (264-RRRO)

- The rate per seed for soybeans, cotton and field corn should be corrected to reflect the AOSA recommendation of 4000 seeds per pound for soybean, 3600 seeds per pound for cotton and 1360 seeds per pound for field corn.
- Under the potato instructions for in-furrow treatment in combination with seed piece treatment the application rate column in the table should be revised to read as follows. "Apply a minimum of 0.4 fl oz per 1,000 row feet (4 ml per 100 row meters) up to a maximum in-furrow application of 9.2 fl oz per acre."
- The crop rotation restriction should be revised to specify the following. "Crops for which there are registered use of penflufen, which includes alfalfa, potatoes (Crop Subgroup 1C), legume vegetables (Crop Group 6/7), cereal grains (Crop Group 15/16), and oil seeds (Crop Group 20) may be replanted at any time. All other crops may be planted no less than 30 days after planting treated seeds."

PENPRO 118FS (264-RREG)

- The crop rotation restriction should be revised to specify the following. "Crops for which there are registered use of penflufen, which includes alfalfa, potatoes (Crop Subgroup 1C), legume vegetables (Crop Group 6/7), cereal grains (Crop Group 15/16), and oil seeds (Crop Group 20) may be replanted at any time. All other crops may be planted no less than 30 days after planting treated seeds."

PENCLO 273.5FS (264-RREL)

- The crop rotation restriction should be revised to specify the following. "Crops for which there are registered uses of both clothianidin and penflufen, which includes canola, cotton, cereal grains except rice, mustard seed, potato (Crop Subgroup 1C) and soybeans may be replanted at any time. Grasses, non-grass livestock feeds, dried beans and dried peas may be planted no less than 30 days after planting treated seeds. Do not plant any other crop in the treated area for at least twelve months after treated seeds are planted."

PENRED 240FS (264-RREN)

- The rate per seed for soybeans, cotton and field corn should be corrected to reflect the AOSA recommendation of 4000 seeds per pound for soybean, 3600 seeds per pound for cotton and 1360 seeds per pound for field corn.
- Under the potato instructions for in-furrow treatment in combination with seed piece treatment the application rate column in the table should be revised to read as follows. "Apply a minimum of 0.4 fl oz per 1,000 row feet (4 ml per 100 row meters) up to a maximum in-furrow application of 9.2 fl oz per acre."
- The crop rotation restriction should be revised to specify the following. "Crops for which there are registered use of penflufen, which includes alfalfa, potatoes (Crop Subgroup 1C), legume vegetables (Crop Group 6/7), cereal grains (Crop Group 15/16), and oil seeds (Crop Group 20) may be replanted at any time. All other crops may be planted no less than 30 days after planting treated seeds."

PENCLOTRIME 310.68FS

- The crop rotation restriction should be revised to specify the following. "Areas planted with treated seed may be replanted immediately with canola, cotton, corn (field, pop and sweet), cereal grains except rice, mustard, rapeseed, sorghum, soybean, and potatoes (tuberous and corm subgroup 1C). These areas may also be replanted no less than 30 days after planting treated seeds with grasses, non-grass livestock feeds, dried beans, fruiting vegetables (including cucurbits), leafy vegetables (including brassica vegetables) and sugar beets. Do not plant any other crop in the treated area for at least twelve months after treated seeds are planted.

PENTRI 308FS

- The rate per seed for soybeans needs to be corrected to reflect the appropriate rate and AOSA recommendation of 4000 soybean seeds per pound.
- The rate per 100 lbs of seed and rate per seed for field corn should reflect the same application rate. Further, the AOSA recommendation of 1260 seeds per pound for field corn should be incorporated into the rate per seed calculation.
- The rate per 100 lbs of seed and rate per seed for cotton should reflect the same application rate. Further, the seeds per pound on the label should be revised to reflect 3600 cotton seeds per pound.
- The crop rotation restriction should be revised to specify the following. "Crops for which there are registered uses of both trifloxystrobin and penflufen, which includes barley, corn, oats, potato, rice, soybean and wheat may be replanted at any time. All other crops may be planted no less than 30 days after planting treated seeds."

3.0 Background

Bayer CropScience is seeking registration for the new active ingredient, penflufen (N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide). Penflufen is a fungicide intended for use as a seed treatment and in-furrow application on potatoes and for use as a seed treatment in legume vegetables, cereal grains, oilseeds and alfalfa. There are

seven end-use products associated with this petition. The formulations and use patterns are discussed in detail in the "Directions for Use" section of this memorandum.

Concurrently with the requested registration, Bayer CropScience is seeking the establishment of tolerances for residues of penflufen in the U.S. for the following commodities:

Tuberous and Corm Vegetable (Crop Sub-Group 1C)	0.01ppm
Legume Vegetables, Succulent or dried (Crop Group 6)	0.01ppm
Foliage of Legume Vegetables, including soybeans (Crop Group 7)	0.01ppm
Soybean, seed	0.01ppm
Cereal Grains (Crop Group 15)	0.01ppm
Forage, fodder and straw of Cereal grains	0.01ppm
Oilseeds (Crop Group 20)	0.01ppm
Cotton, gin by-products	0.01ppm
Alfalfa, Forage and Hay	0.01ppm

Penflufen was submitted as a global review chemical simultaneously to the regulatory authorities in the U.S (EPA), Canada (PMRA) and Australia (AMPV). AMPVA had the lead for review of the metabolism, confined rotational crop, storage stability and analytical method study volumes. EPA had the lead for review of the field trials, processing studies and rotational crop field studies specific to North America.

The chemical and physical properties for penflufen are summarized in the tables below. The structures of penflufen metabolites are shown in Attachment 1, Table A2.

Table 3.1. Test Compound Nomenclature

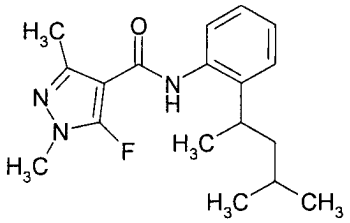
Chemical Structure	
Empirical Formula	$C_{18}H_{24}FN_3O$
Common Name	Penflufen
Company experimental name	BYF 14182
IUPAC name	N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide
CAS Name	1*H*-Pyrazole-4-carboxamide, N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-
CAS Registry Number	494793-67-8
End-use product/EP	PEN 240FS, PENRED 240FS, PENCLO 273.5FS), PENTRI 308FS), PENCLOTRIME 310.68FS, PENPROME 177FS
Chemical Class	Carboxamide
Known Impurities of Concern	None

Table 3.2. Physical/Chemical Properties of Penflufen		
Parameter	**Value**	**Reference**
Molecular Weight	317.41 g/mol	MRID No. 48023535
pH	6.7 (1% suspension in distilled water @ 22°C)	MRID No. 48023525
Water solubility (20°C)	@ pH 4 = 11.0 mg/L @ pH 7 = 10.9 mg/L @ pH 9 = 11.2 mg/L	MRID No. 48023535
Solvent solubility (20°C)	Solvent — g/L methanol — 126 n-heptane — 1.6 toluene — 62 dichloromethane — >250 acetone — 139 ethylacetate — 96 dimethyl sulfoxide — 162	MRID No. 48023536
Vapor pressure (25°C)	9.0×10^{-9} torr	MRID No. 48023537
Dissociation constant, pKa	No dissociation constant (pKa) was found in aqueous solution of penflufen in the range of 1<pH<12. The molecule has no structural moieties which are prone to dissociate.	MRID No. 48023532
Henry's law constant	1.04×10^{-10} atm·m^3/mol	MRID No. 48023539
Octanol/water partition coefficient, log K_{OW} (25°C)	@pH 7 = 3.3	MRID No. 48023534

4.0 Directions for Use (860.1200)

There is one technical product, Penflufen TC (264-RRRI) and seven end use products associated with this petition. Use of penflufen is limited to seed treatment on all crops, with the exception of potatoes. Both seed treatment and a single in-furrow application of penflufen to potatoes are permitted. The detailed use pattern by crop is shown in Table 3.1 and the end use products with their specific label restrictions are shown in Table 3.2.

Table 3. 3. Summary of Directions for Use of Penflufen				
Applic. Timing, Type, and Equip.	**Formulation**	**Use Rates**	**PHI (days)**	**Use Directions and Limitations**
		Alfalfa		
Slurry or mist-type seed treatment	PENRED 240FS PENTRI 308FS PENPROME 177FS PEN 240FS	0.015 lb ai/100 lb seed (15 g ai/100 kg seed)	NS	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Rotational crop restrictions as detailed in Appendix D.

Table 3. 3. Summary of Directions for Use of Penflufen

Applic. Timing, Type, and Equip.	Formulation	Use Rates	PHI (days)	Use Directions and Limitations
Potato (Tuberous and Corm Crop Subgroup 1C)				
Apply as a dilute spray to seed pieces	PENRED 240FS PENCLO 273.5FS PENPRO 118FS PEN 240FS	0.002 lb ai/100 lb seed (2 g ai/100kg seed) may be combined with in-furrow application on PENRED 240FS and PEN 240 FS labels	NS	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Rotational crop restrictions as detailed in Appendix D.
Ground application as in-furrow spray	PENRED 240FS PEN 240 FS	0.12 lb ai/A may be combined with seed piece treatment application	NS	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Rotational crop restrictions as detailed in Appendix D.
Legume Vegetables Including Soybean (Crop Group 6C)				
Slurry or mist-type seed treatment	PENRED 240FS PENTRI 308FS PENPROME 118 FS (dried only) PEN 240 FS	0.005 lb ai/100 lbs seed (5 g ai/100 kg seed)	NS	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Rotational crop restrictions as detailed in Appendix D.
Cereal Grains (Crop Group 15)				
Slurry or mist-type seed treatment	PENRED 240FS PENTRI 308FS (wheat, corn, rice only) PENPRO 118FS (wheat only) PENPROME 177FS (barley, wheat, triticale and rice only) PEN 240FS	Cereal grains, except corn, and sorghum 0.005 lb ai/100 lbs seed (5 g ai/100 kg seed) Corn, sorghum 0.010 lb ai/100 lbs seed (10 g ai/100 kg/seed)	NS	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Rotational crop restrictions as detailed in Appendix D.

Table 3. 3. Summary of Directions for Use of Penflufen

Applic. Timing, Type, and Equip.	Formulation	Use Rates	PHI (days)	Use Directions and Limitations
		Oilseeds (Crop Group 20)		
Slurry or mist-type seed treatment	PENRED 240FS PENTRI 308FS (cotton only) PENCLOTRIME 310.68FS (canola, rape, mustard only) PENCLO 273.5FS (cotton only) PEN 240FS (cotton, sunflower, safflower only)	All oilseeds, except cotton 0.015 lb ai/100 lbs seed (15 g ai/100 kg seed) Cotton 0.010 lbs ai/100 lbs seed (10 g ai/100 kg seed)	NS	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Rotational crop restrictions as detailed in Appendix D.

Table 3.2. Penflufen End Use Products

EPA Reg No.	Product	Composition	Labeled crops	Proposed Restrictions	Co-Formulants[1]
264-RRRO	PEN 240FS	22.7% penflufen 2 lbs penflufen/gal	Alfalfa, dried and succulent legume vegetables including soybeans, cereal grains, cotton, sunflower, safflower, and potato (seed piece treatment and in-furrow)	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Registered seed treatment crops and potatoes may be replanted at any time. All other crops may be planted after 30 days.	None
264-RREE	PENPROME 177FS	3.59% penflufen 0.32 lb penflufen/gal	Alfalfa, dried legume vegetables including soybeans, barley, wheat, triticale, and rice.	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Crops on this label or for which tolerances exist for penflufen may be replanted at any time. All other crops may be planted after 30 days.	Prothioconazole and Metalaxyl
264-RREG	PENPRO 118FS	9.35% penflufen 0.83 lb penflufen/gal	Wheat, potato seed piece treatment	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Crops on this label and other crops for which tolerances exist for penflufen may be replanted at any time. All other crops may be planted after 30 days.	Prothioconazole
264-RREL	PENCLO 273.5FS	6.0% penflufen 0.56 lb penflufen/gal	Cotton, potato seed piece treatment	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Crops on this label, and other crops for which tolerances exist for clothianidan and penflufen may be replanted at any time. Grasses, non-grass animal feeds, dried beans and dried peas may be planted after 30 days. Do not plant any other crop in the treated area for at least twelve months after treated seeds are planted.	Clothianidin

Table 3.2. Penflufen End Use Products

EPA Reg No.	Product	Composition	Labeled crops	Proposed Restrictions	Co-Formulants[1]
264-RREN	PENRED 240FS	22.4% penflufen 2 lbs penflufen/gal	Alfalfa, dried and succulent legume vegetables including soybean, cereal grains, and oilseeds, potatoes (seed piece treatment and in-furrow)	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Registered seed treatment crops and potatoes may be replanted at any time. All other crops may be planted after 30 days.	None
264-RRER	PENCLOTRIME 310.68FS	0.82% penflufen 0.09 lb penflufen/gal	Canola, rapeseed and mustard seed	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Areas planted with treated seed may be replanted immediately with canola, cotton, corn (field, pop and sweet), cereal grains except rice, fruiting vegetables (including cucurbits), leafy vegetables (including brassica vegetables), mustard, rapeseed, sorghum, soybean, sugar beet, tuberous and corm vegetables. These areas may also be replanted after 30 days with grasses, non-grass animal feeds, and dried beans. Do not plant any other crop in the treated area for at least four months after treated seeds are planted.	Clothianidin, trifloxystrobin, metalaxyl
264-RREU	PENTRI 308FS	13.3% penflufen 1.28 lb penflufen/gal	Alfalfa, legume vegetables including soybeans, wheat, corn, sorghum, cotton and rice	Do not use for feed, food or oil purposes. Store away from feeds and foodstuffs. Crops on this label and other crops for which tolerances exist for trifloxystrobin and penflufen may be replanted at any time. All other crops may be planted after 30 days.	Trifloxystrobin

[1] Co-formulants are listed for informational purposes. This review addresses penflufen only.

Conclusions. The submitted labels are adequate to allow evaluation of the submitted residue data relative to the proposed uses.

Recommended label revisions are discussed in Section 2.3, above.

5.0 Summary of Plant and Livestock Metabolism Studies

5.1 Nature of the Residue – Plants (860.1300)

Appendix 1, APVMA Core Metabolism and Storage Stability Study Summaries, March 2011

Plant metabolism data were submitted for potato (seed treatment and in-furrow applications), wheat (seed treatment), soybean (seed treatment), and rice (at transplant) to support the requested new uses of penflufen. Studies for all commodities reflected labeling in both the phenyl and pyrazole rings, application rates were equal to, or exaggerations of the currently proposed use rates, and application techniques reflect the requested application patterns. Adequate storage stability data were provided; acceptable extraction efficiencies and identification were achieved.

Sufficient documentation on the field and analytical portions of the study were provided. The metabolism results for each crop are summarized briefly below. Details of each metabolism study can be found in Appendix 1.

Potato metabolism studies

The metabolism of penflufen was investigated in potatoes treated with penflufen labeled in the phenyl and pyrazole rings. Additionally, studies for each label were conducted reflecting both seed treatment (~0.005 lb ai/100 lbs seed) and in-furrow (~0.5 lbs ai/A) applications at rates approximately twice the currently proposed use pattern. Mature tubers were harvested from all four applications and potato leaves were harvested from the pyrazole label in-furrow application. No significant differences were noted either based on label position or on application technique. Total radioactive residue (TRR) was low in all tuber samples with the in-furrow tubers having higher residues likely due to a higher application rate. The major residue in tubers was the parent compound at ~20-30% of the TRR; minor amounts of penflufen-3-hydroxybutyl (Pen-3HB) were found from the in-furrow application of phenyl labeled penflufen at 12% of the TRR. Other metabolites identified were all <10% of the TRR. In pyrazole treated potato leaves from the in-furrow application, the TRR was significantly higher in the leaves than in the tubers from the same study, though the TRR in the leaves was still at low levels. The major residue in the leaves was Pen-3HB at 19% of the TRR and penflufen-3-hydroxybutyl glucoside at 11% of the TRR. All other identified metabolites were <10% of the TRR. Extractability of the residues in these studies was high and the identification acceptable. Two routes of degradation are postulated for penflufen in potatoes: 1) substitution of glutathione for fluorine in the pyrazole ring followed by hydrolysis of the glutathione moiety to cysteine; and 2) hydroxylation of the third carbon on the butyl substituent, followed by conjugation with glucose and malonic acid.

Wheat metabolism studies

The metabolism of penflufen was investigated in spring wheat treated with penflufen labeled in the phenyl and pyrazole rings. Studies for each label were conducted reflecting seed treatment at 0.05 lbs ai/100 lbs seed (1x the currently proposed rate) and 0.5 lbs ai/100 lbs seed (10x the currently proposed rate). Forage, hay, grain and straw samples were collected and analyzed. The TRR in grain from both application rates and labels was very low precluding attempts at identification. Higher TRR values were observed in forage, hay and straw with residues being highest in straw, followed by hay and forage. The major residue in forage, hay and straw was penflufen-3-hydroxybutyl-malonyl-glucoside at ~20-35% of the TRR and 4-hydroxybutyl-malonyl-glucoside at ~10–20% of the TRR. The parent compound and other minor metabolites were identified and all were <10% of the TRR. Of note, in the pyrazole ring labeled study, very minor amounts of the cleavage product, penfulufen-pyrazole-4-carboxamide (Pen-PCX) were noted in hay and straw. In the phenyl ring labeled study no metabolites specific to the phenyl ring were detected. Extractability of the residues in these studies was high and the identification acceptable. Three routes of degradation are postulated for penflufen in wheat: 1) substitution of glutathione for fluorine on the pyrazole ring followed by hydrolysis of the glutathione moiety to cysteine; 2) hydroxylation of the third or fourth carbon on the butyl substituent, followed by conjugation with glucose and malonic acid; and 3) cleavage of the N-phenyl linkage to yield Pen-PCX.

Soybean metabolism studies

The metabolism of penflufen was investigated in soybeans treated with penflufen labeled in the phenyl and pyrazole rings. Studies for each label were conducted reflecting seed treatment at 0.05 lbs ai/100 lbs seed (1x the currently proposed rate) and 0.5 lbs ai/100 lbs seed (10x the currently proposed rate). Soybean forage, hay and seed were collected and analyzed. The TRR in soybean seed was low with the highest TRR in forage followed by hay. The major residue in seed included penflufen-homoglutathione (Pen-HGT) at 2–77% of the TRR and penflufen-desmethyl-dicarboxylic acid (pyrazole ring only) at 65% of the TRR. In forage the major residues were Pen-HGT at 56-60% of the TRR and cysteine at 10–13% of the TRR. In hay the major metabolites included Pen-HGT at 21–46% of the TRR, penflufen-3-hydroxybutyl-malonyl-glucoside at 3–38% of the TRR and parent compound (phenyl ring label study only) at 14% of the TRR. Other minor metabolites were identified and all were <10% of the TRR. Extractability of the residues in these studies was high and the identification acceptable. Three routes of degradation are postulated for penflufen in wheat: 1) hydrolysis of the fluorine substituent on the pyrazole ring, followed by glutathione conjugations and subsequent hydrolysis of the glutathione moiety; 2) hydroxylation of the third carbon on the butyl substituent, followed by conjugation with glucose and malonic acid; and 3) cleavage of the N-phenyl linkage followed by hydrolysis of the resulting amide to carboxylic acid, oxidation of the C3-methyl substituent, and loss of the N-methyl substituent to yield penflufen-desmethyl-dicarboxylic acid.

Rice metabolism studies

The metabolism of penflufen was investigated in rice treated with penflufen labeled in the phenyl and pyrazole rings. Studies for each label were conducted reflecting soil treatment at transplant at 0.45 lbs ai/A. Rice kernels, husks and straw were collected and analyzed. The TRR in kernels was low with high levels of TRR found in straw and moderate residues found in husks. The major residue in seed included the parent compound at 20-31% of the TRR and Pen-3HB at 20-23% of the TRR. In rice husks the major residue was parent at 15-27% of the TRR and Pen-3HB at 23-24% of the TRR. Other minor metabolites were identified in kernels and husks and all were <10% of the TRR. In rice straw multiple metabolites were identified, with no metabolite present at levels greater than 6% of the TRR. Extractability of the residues in these studies was high and the identification acceptable. Three routes of degradation are postulated for penflufen in rice: 1) hydrolysis of the fluorine substituent on the pyrazole ring, followed by glutathione conjugations and subsequent hydrolysis of the glutathione moiety; 2) hydroxylation of the third carbon on the butyl substituent, followed by conjugation with glucose and malonic acid; and 3) cleavage of the N-phenyl linkage followed by hydrolysis of the resulting amide to carboxylic acid, oxidation of the C3-methyl substituent, and loss of the N-methyl substituent to yield penflufen-desmethyl-dicarboxylic acid.

Conclusions. Plant metabolism data were submitted, reviewed and found to be scientifically acceptable. The metabolic pathway in potatoes, wheat, soybeans and rice is substantially similar. Following seed treatment or in-furrow use of penflufen in potatoes, wheat, soybeans and rice, degradation appears to follow three major pathways: 1) substitution of glutathione for fluorine on the pyrazole ring followed by hydrolysis of the glutathione moiety to cysteine; 2) hydroxylation of the third or fourth carbon on the butyl substituent, followed by conjugation with glucose and malonic acid; and 3) cleavage of the N-phenyl linkage. In all metabolism studies, aniline or aniline related metabolites were not identified.

While the proposed metabolic pathways for these crops are similar, in the absence of data on a fruiting vegetable, this data set is not considered adequate to define the nature of the residue in all plants. Further, since the application techniques were limited to seed treatment, in-furrow or at transplant (rice), these data will not support foliar uses of penflufen on agricultural crops. However, the submitted metabolism data are considered adequate to support the requested seed treatment uses on alfalfa, legume vegetables, cereal grains, oils seeds and the use on potatoes as a seed piece treatment and a single in-furrow application.

5.2 Nature of the Residue – Livestock (860.1300)

Appendix 1, APVMA Core Metabolism and Storage Stability Study Summaries, March 2011

Livestock metabolism studies were submitted for the hen (poultry) and lactating goat (ruminant) for penflufen to support the requested new uses. Studies in both animals reflected labeling in both the phenyl and pyrazole rings. The metabolism results are summarized briefly below. Details of each metabolism study can be found in Appendix 1.

Poultry metabolism studies

The metabolism of penflufen in poultry was investigated using laying hens orally dosed at a rate equivalent to 25-27 ppm in the feed of pyrazole or phenyl ring labeled penflufen. Twelve hens, six dosed with pyrazole ring labeled penflufen and six dosed with phenyl ring labeled penflufen were dosed 14 times at 24 hour intervals and sacrificed about six hours after the last dose. Total radioactivity was measured in the excreta and eggs daily, as well as in the poultry muscle, fat, liver and skin at sacrifice. The majority of the administered dose was recovered in the excreta. Residues in eggs increased linearly reaching a plateau between day 6 and 8. The highest tissue TRR values were measured in the liver and kidney, with lower levels in the skin, fat and muscle. The major residue in eggs was the parent compound at 12% of the TRR, with multiple minor metabolites detected, all at <10% of the TRR. The major residue in fat was parent compound, which was the only compound identified at 74-78% of the TRR. In muscle, the only major metabolite identified was 3,4'-dihydroxy-keto-glucuronide at 10% of the TRR, no parent was detected in muscle. Low levels of various minor metabolites were identified in muscle, all below 10% of the TRR. In liver, no metabolite greater than 10% was identified and parent was not detected even as a minor metabolite.

No significant difference in metabolic profile was seen between the pyrazole and phenyl ring labeled studies. Penflufen is extensively metabolized in the laying hen with over 50 metabolites identified or characterized in the different tissues. Parent was a major metabolite only in fat and eggs. The main metabolic pathways in the hen are N-demethylation in the pyrazole ring, hydroxylation at the various positions of the molecule, further oxidation of hydroxyl groups forming keto and carboxylic acid groups, oxidative cleavage of the alkyl side chain forming an acetyl compound and conjugations of the hydroxyl group in the 4'-position of the phenyl ring with glucuronic acid.

Ruminant metabolism studies

The metabolism of penflufen in ruminants was investigated using lactating goats orally dosed at a rate equivalent to 48 ppm in the feed. Two goats, one dosed with pyrazole ring labeled penflufen and one dosed with phenyl ring labeled penflufen were dosed 5 times at 24 hour intervals and

sacrificed about twenty four hours after the last dose. Total radioactivity was measured in the milk and excreta at timed intervals as well as in liver, kidney, muscle and fat at sacrifice. The majority of the administered dose was recovered in the excreta. The highest tissue TRR values were measured in liver, followed by kidney, fat and muscle. Residues in milk reached a plateau about 32 hours after the first dose was administered. In milk, the major residues were 2,3,4'-trihydroxy (isomer 1) at 17- 4% of the TRR, 3,4'-dihydroxy at 14-16 % of the TRR, and 2,3,4'-trihydroxy (isomer 2) at 10% of the TRR. Additional minor metabolites were identified at <10% of the TRR. In muscle, multiple minor metabolites were identified with 3,4'-dihydroxy as the only metabolite >10% of the TRR at 15-18%. In fat, 3,4'-dihydroxy-glucuronide and 3,4'-dihydroxy were identified at 15 and 14% of the TRR, respectively. Multiple minor metabolites were identified in fat, all <10% of the TRR. In liver multiple metabolites were identified with 3,4'-dihydroxy-glucuronide being the only metabolite >10% of the TRR at 10-15%. Likewise in kidney, multiple metabolites were identified with pentanoic acid (isomer 2) and 3,4'-dihydroxy-glucuronide being the only metabolites >10% of the TRR at 16–17% and 10-13%, respectively.

No substantive difference in metabolic profile was seen between the pyrazole and phenyl ring labeled studies. Penflufen is extensively metabolized in the ruminant as demonstrated by the high level of identified metabolites present at low levels (<10% of the TRR). The main metabolic pathways in the ruminant are N-demethylation in the pyrazole ring, hydroxylation at the various positions of the molecule, further oxidation of the hydroxyl group in the 2-position of the alkyl side chain forming a keto group, oxidation of a terminal methyl group of the alkyl side chain to a carboxylic acid group, and conjugation of the hydroxyl group in the 4'-position of the phenyl ring with glucuronic acid.

Conclusions. Penflufen is extensively metabolized in the hen and lactating goat. The metabolic pathways in poultry and ruminants appear similar. No difference in metabolic profile was noted between the pyrazole and phenyl ring labeled studies. The main metabolic pathways in livestock involve N-demethylation in the pyrazole ring, hydroxylation at various positions in the molecule, oxidation to keto and to carboxylic acid groups, conjugation with glucuronic acid and cleavage of the N-phenyl and carboxamide bond. Aniline or aniline related metabolites were not identified in either livestock metabolism study.

The submitted livestock metabolism studies adequately address the requirement to elucidate the nature of the residue in livestock for penflufen.

5.3 Confined Accumulation in Rotational Crops (860.1850)

Appendix 1, APVMA Core Metabolism and Storage Stability Study Summaries, March 2011

In a confined rotational crop study (MRID No. 48023738), [pyrazole-3-^{14}C]-penflufen, was applied to containerized bare soil at a rate of 0.436 lbs ai/A (532 g ai/ha). The soil surface was treated directly with the formulated product. Three rotational crops, soybean, turnip and wheat, were planted 30 (1st rotation), 157 (2nd rotation) and 377 (3rd rotation) days after soil application. Samples of wheat forage, hay, straw and grain, soybean forage, hay and seed, and turnip roots and leaves were collected at growth stages appropriate for normal commercial harvest.

Total radioactive residues (TRR) in wheat forage, hay, and straw and in soybean hay were significantly higher than in other plant matrices. TRRs in forages/foliages generally increased at the 157-day plant back interval (PBI), and then remained steady or were slightly lower at the 377 day PBI. TRR values in grains, and seeds were similar at the first and second PBIs and decreased significantly at the 377-day PBI. TRR values in the turnip roots and tops declined steadily over time. The TRR values for all rotational crop matrices are shown in the following table.

Table. 5.3.1 TRR (mg/kg) in Rotational Crop Matrices Following Soil Application at 0.436 lbs ai/A

Commodity	First rotation (30-day PBI)	Second rotation (157 day PBI)	Third rotation (377 day PBI)
Wheat forage (BBCH 32-36)	0.131	0.176	0.153
Wheat hay (BBCH 71-75)	0.901	0.477	0.401
Wheat grain (BBCH 89-92)	0.078	0.083	0.027
Wheat straw (BBCH 89-92)	3.947	1.225	0.676
Soybean forage (BBCH 25-29)	0.217	0.461	0.149
Soybean hay (BBCH 73-75)	0.842	1.227	0.533
Soybean seed (BBCH 88-89)	0.220	0.290	0.063
Turnip roots (BBCH 49)	0.079	0.025	0.012
Turnip leaves (BBCH 49)	0.256	0.122	0.054

Parent compound was only a minor residue component, and then only in some matrices. Fifteen metabolites were identified. In wheat forage, hay, and straw, the conjugated hydroxy metabolites Pen-3HB malonyl-glucoside, Pen-4HB malonyl-glucoside, and Pen-3HB glucoside were prominent, while in grain all the metabolites identified were carboxamide and carboxylic acid cleavage products, notably Pen-PCX, Pen-desmethyl-dicarboxylic acid, and Pen-D3C. In soybean seed, the metabolite profile was similar to that of wheat grain, but with the carboxylic acid cleavage products clearly dominating the amides. In soybean forage and hay, the conjugate Pen-HGT was one of the most significant metabolites, with its subsequent metabolites also being identified. The carboxylic acid cleavage products and glucoside and malonyl glucoside conjugates of hydroxylated metabolites were also moderately significant in soybean forage and hay. In turnip leaves, Pen-3HB malonyl-glucoside, Pen-4HB malonyl-glucoside, and Pen-3HB glucoside were very significant components of the residue, with the amide cleavage products Pen-PCX and Pen-desmethyl-pyrazole-4-carboxamide also being prominent residue components. In turnip roots, the conjugate Pen-glutathione and subsequent metabolites were significant, along with the carboxamide cleavage products.

Four key metabolic pathways were identified in the rotational crops tested. These were (i) substitution of glutathione or homoglutathione for fluorine on the pyrazole ring followed by hydrolysis of the glutathione moiety to cysteine, (ii) hydroxylation of the third or fourth carbon on the butyl substituent, followed by conjugation with glucose and malonic acid, (iii) cleavage of the amide linkage yielding a carboxylic acid, with subsequent *N*-demethylation and oxidation and loss of the C3-methyl group and conjugation with serine, and (iv) cleavage at the *N*-phenyl linkage to yield penflufen-pyrazole-4-carboxamide, with subsequent *N*-demethylation.

In a second confined rotational crop study (MRID No. 48023740) [phenyl-UL-$^{13}C_6$/ ^{14}C] and [pyrazole-3-^{14}C]penflufen were each applied separately by spray application to containerized bare soil at a rate of 0.0089 lbs ai/A (10g ai/ha). Three rotational crops, spring wheat, Swiss chard and turnips were each sown at 30 (1st rotation), 139 (2nd rotation) and 287 (3rd rotation) days after application. Samples of wheat forage, hay and immature Swiss chard were sampled prior to normal harvest; all other samples (wheat straw and grain, Swiss chard, turnip leaves and roots) were harvested at maturity.

Total radioactive residues in the harvested samples were low. As in primary crops, the highest TRR values were in the forage, hay and straw of wheat. The TRR in wheat grain, immature and mature Swiss chard and turnip leaves and roots were all significantly below 0.01 ppm at 30-days and not detectable at the two longer planting intervals. The TRR values are shown in Table 5.3.2, below.

Table 5.3.2 TRRs in Confined Rotational Crops Following Soil application of Penflufen

Plant back Interval	Wheat TRR (mg/kg)				Swiss chard TRR (mg/kg)		Turnip TRR (mg/kg)	
	forage	hay	straw	grain	immature	mature	leaves	roots
[phenyl-UL-$^{13}C_6$/ ^{14}C]penflufen applied at 0.0089 lbs ai/A								
30-days	0.008	0.022	0.059	0.001	0.002	0.004	0.006	0.002
139-days	0.011	0.014	0.018	0.003	n.d.	n.d.	n.d.	n.d.
287-days	0.007	0.016	0.019	0.001	n.d.	n.d.	n.d.	n.d.
[pyrazole-3-^{14}C]BYF 14182 applied at 0.0089 lbs ai/A								
30-days	0.009	0.027	0.058	0.001	0.003	0.004	0.009	0.003
139-days	0.011	0.014	0.040	0.004	n.d.	n.d.	n.d.	n.d.
287-days	0.009	0.020	0.022	0.002	n.d.	n.d.	n.d.	n.d.

n.d. = not determined

Samples with TRRs above 0.01 mg/kg (wheat hay and straw, and forage of the second rotation) were extracted with acetonitrile/water and the metabolic profiles after HPLC analysis compared with those from previous confined rotational studies involving application at 0.45 lb ai/A (500 g ai/ha). Parent compound accounted for ≤12% of the TRR (≤0.002 mg/kg) in the first and second rotations and was not found in the third rotation for either label. Seven metabolites were identified, 2 of which were specific to the pyrazole label. No metabolites specific to the phenyl label were found. The identified metabolites were Pen 3-HB glucoside, Pen 3-HB malonyl glucoside, Pen-4HB malonyl glucoside, Pen-hydroxyl-mercapto-lactic acid, Pen-succinyl cysteine, Pen-PCX, and Pen-D3C. None of the identified metabolites accounted for more than 0.009 mg/kg in any sample. In all 40–83% of the TRR was identified. Eleven unknown metabolites were characterized, with none accounting for more than 0.009 mg/kg in any sample. Radioactivity remaining in the solids after extraction ranged from about 9 to 23% of the TRR and was ≤0.010 mg/kg (for most of the samples ≤0.004 mg/kg).

Four degradation pathways are proposed for penflufen: (i). Hydroxylation at the 3- or 4- position of the alkyl side chain followed by conjugation with glucose and malonic acid. (ii). Conjugation with glutathione via substitution of the fluorine atom followed by metabolic degradation of the glutathione moiety. (iii). Cleavage of the amide bond followed by N-demethylation and oxidation of the remaining methyl group to a carboxylic acid. (iv). Cleavage of the N-phenyl bond followed

by N-demethylation to release the pyrazole-4-carboxamide.

Conclusions. Confined rotational crop data were submitted, reviewed and found to be scientifically acceptable. Two separate studies were conducted at different application rates and the metabolism using both phenyl- and pyrazole-labeled penflufen was investigated. In accordance with OCSPP 860.1850 guidance, the confined rotational crop study included a small grain (wheat), leafy vegetable or soybeans (Swiss chard and soybeans) and a root crop (turnip). No significant differences were noted between the two labels or the different rate studies. The metabolic pathway in rotational crops appears to be substantially similar for the different rotated crops, and also is substantially similar to the metabolism in primary crops.

Following application to bare soil, the degradation of penflufen in rotational crops appears to follow four major pathways: 1) hydroxylation at the 3- or 4- position of the alkyl side chain followed by conjugation, 2) conjugation with glutathione via substitution of the fluorine atom followed by metabolic degradation of the glutathione moiety, 3) cleavage of the amide bond, and 4) cleavage of the N-phenyl bond.

No additional rotational crop data are required to support the requested use of penflufen as a seed treatment on alfalfa, legume vegetables, cereal grains, and oilseeds and as a seed treatment and in-furrow application to potatoes. The registrant is advised that should additional uses be requested that involve significantly higher application rates, additional rotational crop data may be required.

5.4 Residues of Concern Summary and Rationale

ROCKS Memo, D387299, W. Irwin, 6/15/2011

The HED Residues of Concern Knowledgebase Sub-committee (ROCKS) considered the available data on the nature and magnitude of residues in penflufen and has concluded that for plants, the parent compound only be included for tolerance enforcement and dietary risk assessment. At this time, there is no reasonable expectation of finite residues in livestock so the committee had no recommendation on residues of concern in livestock. For drinking water, the ROCKS recommended including the parent, penflufen-3-hydroxybutyl (Pen-3HB), and penflufen-pyrazolyl-AAP. The reasoning behind these recommendations is as follows:

- Hazard Considerations: Technical penflufen displayed low acute toxicity via the oral, dermal and inhalation routes of exposure (Toxicity Categories III and IV). Increased liver weight, hepatocellular hypertrophy, and thyroid hypertrophy were observed in several animal studies throughout the penflufen toxicity database. Reproductive toxicity (delayed sexual maturation) was observed in females in both generations in the rat reproduction study. There are no neurotoxicity or mutagenicity concerns. Mutagenicity studies with penflufen-pyrazolyl-AAP and Pen-3HB were also negative for mutagenic activity. However, penflufen is "suggestive" for carcinogenicity but not sufficient for quantitation of cancer risk in humans. A structure activity analysis of penflufen and its major metabolites using DEREK v.12 did not raise any concerns for toxic effects that were not already observed in the toxicity database.

- Drinking Water: Parent penflufen, and the metabolites Pen-3HB, and penflufen-pyrazolyl-AAP (AAP) were identified as potential major degradates in drinking water. Penflufen is relatively stable in soil degradation studies (t½ > 100 days) and is not susceptible to hydrolysis. Concentrations of the degradates were increasing at the end of the degradations studies precluding accurate measures of half-lives. Therefore, there is a reasonable expectation of exposure to these compounds. Since the structures of the metabolites are similar to the parent, they are assumed to have similar toxicities. Therefore, ROCKS recommended that parent penflufen, Pen-3HB, and penflufen-pyrazolyl-AAP be included as residues of concern for drinking water. In addition, since penflufen is susceptible to photolysis, the ROCKS committee recommended that the metabolites M60 (fluoro acid) and M64 (bis-desmethyl-3-carboxylic acid) be reassessed should there be any uses proposed where aqueous photolysis may be a significant route of environmental dissipation.

- Primary/Rotational crops: The proposed use for penflufen is seed treatment or in-furrow treatment (potatoes only) so the ROCKS recommendation is based on these uses only. Since the metabolic and degradation pathways for primary/rotational crops are similar, all crops will be discussed together.

  Residues identified in the plant metabolism and confined rotational studies included parent, Pen-3HB, Pen-HGT, Pen-PCX, and Pen-bis-desmethyl-3-carboxylic acid (Pen-D3C). Total residues in the plant are low in the primary crop metabolism studies, which reflect the proposed seed treatment uses. In confined rotational crop studies at 3X application rates, some metabolites were in the ppb range (i.e., Pen-3HB); at exaggerated application rates of up to 10X, only low levels of parent were measured in forage materials. Similarly, residues were low or non-detectable in field trials. Of those that were identified, they were largely conjugated and most likely to be found in livestock feedstuffs and are a lesser concern. Based on structure and SAR analysis, the metabolites identified in the plant studies are not likely to be more toxic than the parent penflufen.

  Therefore, due to the low quantities identified, the conjugated nature of the residues that were identified, and likelihood that the residues will be found in livestock feedstuffs at minimal levels, the ROCKS recommended parent only be included for risk assessment and tolerance. If there is gross misuse on primary crops, there is likely to be parent residues that would be an adequate indicator of misuse.

The residues of concern for penflufen are summarized in table 5.4, below.

Table 5.4 Penflufen Residues to be Included in the Risk Assessment and Tolerance Expression[1].

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression for Compliance Monitoring
Plants	Primary Crop	Penflufen	Penflufen
	Rotational Crop	Penflufen	Penflufen
Livestock	Ruminant	Not applicable at this time; no expectation of finite residues in livestock commodities.	Not applicable at this time; no expectation of finite residues in livestock commodities.
	Poultry	Not applicable at this time; no expectation of finite residues in livestock commodities.	Not applicable at this time; no expectation of finite residues in livestock commodities.
Drinking Water		Penflufen plus metabolites penflufen-hydroxybutyl and penflufen-pyrazolyl-AAP	N/A

[1] Residues of concern are relevant to seed treatment and in-furrow (potato) uses only.
Penflufen Parent: *N*-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide
Penflufen-hydroxybutyl: Pen-3HB,
5-fluoro-*N*-[2-(3-hydroxy-1,3-dimethylbutyl)phenyl]-1,3-dimethyl-1*H*-pyrazole-4-carboxamide
Penflufen-pyrazolyl-AAP: *N*-(2-acetylphenyl)-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide

6.0 Residue Analytical Methods (860.1340)

6.1 Data Collection Methods

Appendix 3, U.S. EPA NAFTA GAP Study Summaries, October 2010
Appendix 4, APVM Final Storage Stability Study Summary, August 2011

6.1.1 Analytical Method No. 01057

The storage stability study was conducted using analytical method (AM) No. 01057. The method is briefly described as follows. Samples were extracted into aqueous acetonitrile (ACN) and concentrated before heating with strong acid to hydrolyze the conjugates. The extracts were then neutralized, diluted and the internal standards added. Samples were analyzed by liquid chromatography/triple stage quadrupole mass spectrometry (LC/MS/MS) using a reverse phase system. The method limit of quantitation (LOQ) for penflufen was 0.01 ppm. The calculated limit of detection is 0.003 ppm (⅓ of the LOQ). Extensive method validation data were submitted for AM No. 01057 and these data are shown in tables B.5.2-2 through B.5.2-5 in Appendix 2. The method was validated in sunflower seed prior to conduct of the storage stability study. Method validation and concurrent fortification recovery data gathered during the storage stability study are shown in Table 6.1.1, below.

Table 6.1.1 AM No. 01057 Method Validation and Concurrent Fortification Results for Penflufen[1]

Matrix	Fortification level (mg/kg)	Sample size (n)	Recoveries (%)	Mean (%)	Standard deviation (%)
Method Validation					
Sunflower (seed)	0.01	3	73, 76, 67	72	4.6
	0.10	3	62, 70, 76	69	7.0
Concurrent Fortifications					
Potato (tuber)	0.01	5	90, 77, 97, 77, 78	84	9.2
	0.10	2	92, 85	88	NA
	0.20	10	91, 81, 77, 110, 116, 95, 67, 80, 87, 79	88	15
Lettuce (head)	0.01	5	94, 76, 82, 52, 70	75	16
	0.40	2	108, 112	110	NA
	0.20	10	90, 85, 83, 77, 67, 63, 67, 74, 80, 75	76	8.7
Dry bean (seed)	0.01	5	69, 86, 88, 80, 59	76	12
	0.20	12	63, 64, 59, 74, 76, 114, 107, 75, 80, 85, 64, 65	77	17
Orange (fruit)	0.01	4	90, 80, 77, 83, 79	82	5.1
	0.20	12	89, 90, 87, 79, 79, 92, 101, 75, 90, 68, 82, 76	84	9.1
Wheat (grain)	0.01	5	70, 73, 82, 81, 79	77	5.2
	0.20	15	69, 74, 64, 62, 68, 97, 90, 90, 73, 70, 75, 50, 85, 87, 81	76	13
Wheat (straw)	0.05	5	84, 76, 92, 50, 62	73	17
	1	14	75, 73, 79, 81, 77, 92, 97, 62, 60, 51, 51, 64, 62, 73	69	12
Sunflower (seed)	0.01	4	47, 64, 66, 53	58	9.0
	0.20	12	52, 49, 43, 67, 65, 97, 100, 68, 41, 61, 46, 72	63	19

[1] Recovery data were provided for additional penflufen metabolites; however since those metabolites are not part of the residue of concern, that data is not included here.

Conclusions: The Agency has determined that the residues of concern in plants are the parent compound only; therefore, conclusions are limited to residues of penflufen only. Recoveries of penflufen were highly variable, though generally within the acceptable range of 70–120% in all matrices with the exception of sunflower seed. Consistently low recoveries were demonstrated with sunflower seed. Sufficient chromatograms have been provided and an adequate linearity of response over the range of expected residues has been demonstrated. Based on the submitted concurrent fortification data, the Agency concludes that Method No. 01057 is adequate to detect residues of penflufen, in storage stability samples.

6.1.2 Analytical Method EL-002-P09-01

Crop field trials were conducted in wheat, barley, corn, potato, bean, pea, and soybean and residue samples were analyzed using analytical method EL-002-P09-01. The potato processing study also analyzed for residues of penflufen using EL-002-P09-01. The method is briefly described as follows. Samples are homogenized, extracted twice into aqueous acetonitrile (ACN), and dosed with internal standard. The combined extracts are concentrated before heating with strong acid to

hydrolyze the conjugates. The extracts are then neutralized, and then diluted with 0.5% formic acid. The residues of penflufen and its metabolites are quantitated by liquid chromatography/tandem mass spectrometry (LC/MS/MS).

The method limit of quantitation for penflufen in all matrices was 0.01 ppm. The calculated limit of detection (LOD) is 0.003 ppm (⅓ of the LOQ). Concurrent fortification data were provided for penflufen using method EL-002-P09-01 and are summarized in the tables below.

Table 6.1.2 Concurrent Fortification Data for Penflufen[1]

Crop Matrix	Spike Level (ppm)	Sample Size (n)	Recoveries (%)	Mean % Recovery	Standard % Deviation
Wheat Forage (Field Trial)	0.01	3	74, 70, 75	73	3
Wheat Forage (Processing Study)	0.010	7	92, 93, 89, 94, 96, 86, 101	93	5
	0.050	2	98, 103	100	NA
	0.200	2	96, 94	95	NA
Wheat Grain (Field Trial)	0.01	3	92, 78, 96	89	10
Wheat Grain (Processing Study)	0.010	7	95, 94, 96, 98, 100, 94, 101	97	3
	0.050	2	98, 100	99	NA
	0.200	2	99, 96	97	NA
Wheat Hay (Field Trial)	0.01	4	99, 83, 95, 86	91	8
	0.02	2	89, 96	92	NA
	0.02	2	82, 89	85	NA
Wheat Hay (Processing Study)	0.010	7	108, 99, 98, 85, 93, 94, 89	95	7
	0.050	2	93, 93	93	NA
	0.200	2	95, 91	93	NA
Wheat Straw (Field Trial)	0.01	3	96, 108, 91	98	9
	0.02	3	96, 91, 93	93	2
	0.02	3	82, 85, 92	86	5
Wheat Straw (Processing Study)	0.010	7	96, 98, 105, 106, 97, 81, 89	96	9
	0.050	2	89, 101	95	NA
	0.200	2	95, 99	97	NA
Barley Hay	0.01	7	86, 83, 87, 74, 88, 95, 81	85	6
	0.05	2	97, 84	90	NA
	0.10	3	85, 99, 82	89	9
	0.20	3	92, 98, 96	95	3
Barley Grain	0.01	7	100, 91, 91, 88, 85, 90, 77	89	7
	0.05	2	96, 95	95	NA
	0.20	4	101, 102, 101, 93	99	4
Barley Straw	0.01	7	91, 84, 97, 89, 84, 93, 73	87	8
	0.05	2	94, 97	96	NA
	0.20	4	99, 96, 96, 101	98	3
Corn Fodder	0.01	9	98, 71, 74, 76, 84, 84, 85, 100, 85	84	10
	0.10	3	94, 92, 87	91	4

Table 6.1.2 Concurrent Fortification Data for Penflufen[1]

Crop Matrix	Spike Level (ppm)	Sample Size (n)	Recoveries (%)	Mean % Recovery	Standard % Deviation
Corn Forage	0.010	7	75, 92, 102, 90, 91, 87, 116	93	13
	0.100	4	81, 92, 91, 95	90	6
Corn Grain (Field Trials)	0.010	8	102, 86, 108, 72, 98, 89, 73, 76	88	14
	0.100	4	102, 105, 93, 99	100	5
Corn Grain (Processing Study)	0.025	2	98, 96	97	NA
	0.050	2	98, 97	98	NA
Corn K+CWHR[2]	0.010	7	91, 83, 83, 82, 99, 80, 81	86	7
	0.100	4	94, 90, 94, 95	93	2
Potato Tubers (Field Trials)	0.01	8	105, 92, 90, 87, 102, 95, 99, 82	94	8
	0.10	12	72, 99, 89, 88, 81, 94, 92, 80, 95, 80, 85, 104	88	9
Potato Tubers (Processing Study)	0.010	1	114	NA	NA
	0.100	1	85	NA	NA
Potato Wet Peel	0.010	1	80	NA	NA
	0.100	1	114	NA	NA
Potato Flakes	0.010	1	78	NA	NA
	0.100	1	83	NA	NA
Potato Chips	0.010	1	104	NA	NA
	0.100	1	89	NA	NA
Dry Bean Forage	0.010	4	91, 85, 94, 100	93	6
Dry Bean Hay	0.010	4	112, 91, 98, 94	99	10
Dry Bean Seed	0.010	4	91, 90, 87, 84	88	3
Succulent Pea Seed	0.010	3	99, 93, 96	96	3
Dry Pea Hay	0.010	4	98, 91, 100, 91	95	5
Dry Pea Seed	0.010	4	91, 98, 93, 81	90	7
Dry Pea Vines	0.010	4	83, 90, 88, 96	89	5
Succulent Bean Seed	0.010	3	94, 99, 89	94	5
Soybean Forage (Field Trial)	0.010	1	76	NA	NA
	0.050	1	84	NA	NA
	0.200	1	95	NA	NA
Soybean Forage (Processing Study)	0.010	6	99, 72, 76, 92, 82, 85	85	10
	0.050	2	83, 84	83	NA
	0.100	3	86, 90, 94	90	4
	0.200	2	94, 92	93	NA
Soybean Hay (Field Trial)	0.010	1	109	NA	NA
	0.050	1	94	NA	NA
	0.200	1	99	NA	NA
Soybean Hay (Processing Study)	0.010	7	91, 72, 82, 88, 83, 74, 105	85	11
	0.050	2	78, 77	78	NA
	0.100	1	73	NA	NA
	0.200	2	83, 82	83	NA

Table 6.1.2 Concurrent Fortification Data for Penflufen[1]

Crop Matrix	Spike Level (ppm)	Sample Size (n)	Recoveries (%)	Mean % Recovery	Standard % Deviation
Soybean Seed (Field Trial)	0.010	1	73	NA	NA
	0.050	1	98	NA	NA
	0.200	1	98	NA	NA
Soybean Shelled Immature Seed (Processing Study)	0.010	7	85, 88, 88, 97, 86, 84, 98	89	6
	0.050	2	90, 97	93	NA
	0.100	1	84	NA	NA
	0.200	2	90, 92	91	NA
Soybean Podded Immature Seed (Processing Study)	0.010	7	86, 97, 92, 87, 91, 88, 85	89	4
	0.050	2	89, 83	86	NA
	0.100	1	91	NA	NA
	0.200	2	89, 91	90	NA
Soybean Mature Seed (Processing Study)	0.010	7	85, 83, 75, 94, 77, 75, 82	82	7
	0.050	2	93, 87	90	NA
	0.100	2	90, 95	93	NA
	0.200	2	95, 87	91	NA

[1] Recovery data were provided for additional penflufen metabolites; however since those metabolites are not part of the residue of concern, that data is not included here.
[2] K+CWHR is kernel plus cob with husk removed.
NA is not applicable; standard deviations not calculated for fortification levels with two or fewer samples.

Conclusions: The Agency has determined that the residues of concern in plants are the parent compound only; therefore, conclusions are limited to residues of penflufen only. Concurrent fortification recoveries were acceptable for the parent compound in all matrices. Recoveries of penflufen in all matrices were within the acceptable range of 70% – 120%. Adequate chromatograms have been provided and the linearity of response over the range of expected residues has been demonstrated. Based on the submitted concurrent fortification data, the Agency concludes that Method EL-002-P09-01 is adequate to detect residues of penflufen, the residue of concern, in potatoes, legumes, and cereal grains and in processed potato commodities.

6.2 Enforcement Method

Appendix 2, APVMA Analytical Methods Study Summaries, March 2011

The BayerCrop Science LC/MS/MS method EL-002-P09-03, which is the final method volume which incorporates ILV comments into method EL-002-P09-02, is proposed as a tolerance enforcement method for penflufen. This method employs the same extraction scheme used in the metabolism studies, is a minor modification of EL-002P09-01, which was validated as a data collection method in the field trials and is a minor modification of method AM No. 01057, the original analytical method developed for penflufen.

Bayer method EL-002-P09-03 is described briefly as follows. Samples are homogenized and extracted with 4:1 acetonitrile/water repeatedly. The extracts are cleaned up using solid phase extraction and combined, an external standard is added and the extract is taken to dryness. Hydrochloric acid is added to the dried extract and the solution is heated to hydrolyze any conjugates. The sample is then neutralized with sodium hydroxide, diluted with formic acid in

water, and an isotopically labeled internal standard is added. Penflufen is quantitated by liquid chromatography/triple stage quadrupole mass spectrometry (LC/MS/MS). The method LOQ is 0.01 ppm and the calculated LOD is 0.003 ppm.

Extensive method validation data were submitted for AM No. 01057 and these data are shown in tables B.5.2-2 through B.5.2-5 in Appendix 2. Additionally, concurrent fortification data in potatoes, legumes, and cereal grains is available using method EL-002-P09-01. These data are summarized in tables 6.1.2.1 through 6.1.2.6, above. Both methods employ the same extraction scheme as the proposed enforcement method and differ only in the use of a solid phase extraction clean-up step, which is included in the enforcement method. The proposed enforcement method has been subjected to an ILV as method EL-002-P09-02 (MRID No. 48023709) and minor comments from the ILV have been incorporated into the final version of the method, EL-002-P09-03. The results of the ILV are shown in Table 6.2, below.

Table 6.2 Summary of the ILV Recoveries

Penflufen (BYF-14182) Transition 318.2 → 234.1 (Quantitation Ion)

Matrix	Internal standards		
	Spike Level (ppm)	Recoveries Obtained (%)	Mean ± %CV
Soybean forage	0.01	88.1, 88.3, 89.3, 93.8, 104	92.7 ± 7.3
	0.1	84.1, 91.6, 96.1, 105, 116	98.6 ± 12.5
Soybean seed	0.01	93.5, 94.0, 96.1, 101, 105	97.9 ± 5.1
	0.1	96.1, 96.5, 97.6, 97.7, 102	98.0 ± 2.4

Conclusions. The Agency has considered the submitted data and has reviewed the analytical method, EL-002-P09-03 against the TMV (Tolerance Method Validation) checklist contained in ACB (Analytical Chemistry Branch/BEAD)'s SOP No. 019, Revision 1.0. Adequate recovery data and chromatograms have been provided at the method LOQ, which is also the proposed tolerance level for all crops. The method uses techniques and instrumentation that are considered common technology, including the use of stable, isotopically labeled standards, based on a consult with ACB (email communication from C. Stafford to D. Davis dated 10/20/11). Analysis can be completed in 24 hours and the method does not involve the use of hazardous reagents. The method displayed good linearity, specificity and repeatability and includes the use of a confirmation transition. While specific radiovalidation data were not submitted, the extraction procedure is substantially similar to the procedures used in the metabolism studies; and since good extraction efficiencies were seen in those studies, additional radiovalidation data are not required. The Agency concludes that the LC/MS/MS method , EL-002-P09-03, is an acceptable method to enforce the proposed tolerances for residues of the parent compound, penflufen in/on alfalfa, potatoes, legume vegetables, cereal grains and oilseeds. An enforcement method for livestock commodities is not required at this time.

6.3 Multiresidue Methods (860.1360)

Appendix 2, APVMA Analytical Methods Study Summaries, March 2011

Penflufen and its four metabolites, Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C were tested through a select portion of the FDA-Pesticide Analytical Methods (PAM) Multi-Residue testing program (Protocols A, B, C, D, E and F) in accordance with OCSPP test guideline 860.1360. Testing of all five analytes using Protocol A showed that none of them were naturally fluorescent

and their structures indicated that post-column derivatization to form a fluorescent compound was unlikely to work. Good recoveries could not be achieved for methyl derivatives of the two acid analytes Pen-D3C and Pen-HGT using GC under Protocol B. Under Protocol C for GC of the underivatised analytes, good sensitivity was only achieved for Pen-PCX; however, recoveries on extraction from fatty and non-fatty matrices under Protocols D, E, and F were extremely poor. Testing under Protocol G was not conducted as none of the compounds are substituted urea compounds. Therefore, the US FDA Multi-Residue Method was not suitable for analysis of penflufen or its metabolites.

Conclusions. Penflufen has been subjected to the required analysis by the FDA multi-residue method protocols (MRID No. 48023710). No additional multi-residue method testing is required for this active ingredient at this time. Penflufen is not adequately recovered through any of the current FDA multi-residue protocols.

6.4 Submittal of Analytical Reference Standards (860.1650)

BayerCrop Science provided a stable, isotopically labeled reference standard for the parent compound, penflufen to the EPA National Standard Repository. The standard does not expire until June 2012 (email communication from T. Cole to D. Davis 11/15/11).

Conclusions. The Agency is in receipt of the required penflufen standard. This requirement has been adequately addressed and no further action is required on the part of the registrant.

7.0 Storage Stability (860.1380)

Appendix 4, APVMA Final Storage Stability Summary, August 2011

The registrant submitted an interim storage stability study (MRID No. 48023721), as well as a final study (MRID No. 48516101). Since the final report includes the storage intervals included in the interim report, as well as additional storage intervals, this memorandum addresses only the final report.

A study was conducted to investigate the storage stability of penflufen and its metabolites, Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C in plant matrices when stored under frozen conditions. Samples of potato (tuber), lettuce (head), orange (fruit), dry bean (seed), wheat (grain and straw) and sunflower (seed) were fortified with the test analytes at 0.20 ppm, with the exception of wheat straw which was fortified at 1 ppm. Samples were stored at ≤-18°C and were analyzed after storage intervals of 0, 3–4, 8–9, 16–17, and 26–7 months. At each storage interval levels penflufen and its metabolites were determined using analytical method 01057, which is described in Section 6.1.1, above. After a deep-freezer storage period of 26–27 months mean corrected recovery values ranged from 87–109% for penflufen, 90–103% for Pen-3HB, 85–123% for Pen-HGT, 92–105% for Pen-PCX, and 100–114% for Pen-D3C.

Table 7.1 Storage Stability Data for Penflufen[1]

Commodity	Fortification level (mg/kg)	Storage interval (months)	Recovered residues in stored samples (mg/kg)	Mean recovered residues in stored samples (mg/kg) and mean percent recovery	Mean concurrent recovery (%)	Corrected recovery (%)
Potato (tuber)	0.2	0	0.196, 0.198, 0.193	0.196 (98%)	83	118
		3	0.151, 0.157, 0.158	0.155 (78%)	89	87
		9	0.220, 0.219, 0.220	0.220 (110%)	113	97
		17	0.105, 0.165, 0.168	0.146 (73%)	81	91
		26	0.169, 0.154, 0.160	0.161 (81%)	82	99
Lettuce (head)	0.2	0	0.192, 0.190, 0.193	0.192 (96%)	86	111
		3	0.135, 0.122, 0.145	0.134 (67%)	72	93
		9	0.199, 0.181, 0.177	0.186 (93%)	110	85
		16	0.129, 0.113, 0.104	0.115 (58%)	65	89
		26	0.147, 0.153, 0.151	0.150 (75%)	76	99
Dry bean (seed)	0.2	0	0.115, 0.143, 0.122	0.127 (64%)	62	103
		3	0.151, 0.145, 0.146	0.147 (74%)	75	98
		9	0.135, 0.167, 0.152	0.151 (76%)	111	68
		17	0.167, 0.177, 0.182	0.175 (88%)	78	112
		26	0.151, 0.158, 0.157	0.155 (78%)	71	109
Orange (fruit)	0.2	0	0.201, 0.175, 0.171	0.182 (91%)	89	102
		3	0.165, 0.159, 0.138	0.154 (77%)	79	97
		8	0.193, 0.200, 0.191	0.195 (97%)	97	100
		16	0.157, 0.175, 0.151	0.161 (80%)	83	96
		26	0.159, 0.141	0.150 (75%)	75	100

Table 7.1 Storage Stability Data for Penflufen[1]

Commodity	Fortification level (mg/kg)	Storage interval (months)	Recovered residues in stored samples (mg/kg)	Mean recovered residues in stored samples (mg/kg) and mean percent recovery	Mean concurrent recovery (%)	Corrected recovery (%)
Wheat (grain)	0.2	0	0.140, 0.132, 0.118	0.130 (65%)	69	94
		4	0.148, 0.165, 0.159	0.157 (79%)	65	121
		9	0.188, 0.186, 0.172	0.182 (91%)	94	97
		17	0.171, 0.130, 0.142	0.148 (74%)	82	90
		26	0.164, 0.108, 0.112, 0.117, 0.153, 0.126	0.130 (65%)	75	87
Wheat (straw)	1.0	0	0.759, 0.735, 0.776	0.757 (76%)	76	100
		4	0.745, 0.725, 0.757	0.742 (75%)	79	95
		9	0.963, 0.889, 0.875	0.909 (91%)	95	96
		16	0.604, 0.793, 0.855, 0.711, 0.825, 0.558	0.724 (72%)	56	129
		26	0.651, 0.548, 0.663	0.621 (62%)	66	94
Sunflower (seed)	0.2	0	0.091, 0.125, 0.124	0.113 (57%)	48	119
		4	0.135, 0.128, 0.123	0.129 (65%)	66	98
		8	0.150, 0.146, 0.145	0.147 (73%)	99	74
		17	0.162, 0.113, 0.100	0.125 (63%)	55	114
		27	0.108, 0.100, 0.155	0.121 (61%)	60	100

[1] Storage stability data were provided for additional penflufen metabolites; however since those metabolites are not part of the residue of concern, those data are not included here.

A summary of the storage conditions and duration of storage for the crop field trials included in this submission is shown in Table 7.2.

Table 7.2 Summary of Storage Conditions and Durations for Penflufen Crop Field Trials

Residue	Matrix (RAC)	Storage Temperature (°C)	Actual Study Duration (months)	Limit of Demonstrated Storage Stability
Penflufen	Wheat Forage (Field Trial)	< 0°C	19	26 months based on frozen stability demonstrated in a wide variety of crops including potatoes, lettuce, dry bean, orange, wheat and sunflower seed
	Wheat Forage (Processing Study)	< 0°C	15	
	Wheat Hay (Field Trial)	< 0°C	19	
	Wheat Hay (Processing Study)	< 0°C	14	
	Wheat Grain (Field Trial)	< 0°C	19	
	Wheat Grain (Processing Study)	< 0°C	13	
	Wheat Straw (Field Trial)	< 0°C	19	
	Wheat Straw (Processing Study)	< 0°C	14	
Penflufen	Barley hay	< 0°C	15	
	Barley Straw	< 0°C	14	
	Barley grain	< 0°C	14	
Penflufen	Corn Forage	< 0°C	16	
	Corn K+CWHR	< 0°C	16	
	Corn Grain (Field Trial)	< 0°C	16	
	Corn Grain (Processing Study)	< 0°C	12	
	Corn Stover	< 0°C	14	
Penflufen	Potato Tubers (Field Trial)	< 0°C	19	
	Potato Tubers (Processing Study	< 0°C	16	
	Potato Wet Peel	< 0°C	16	
	Potato Flakes	< 0°C	16	
	Potato Chips	< 0°C	16	
Penflufen	Succulent Bean Seed	< 0°C	17	
	Succulent Pea Seed	< 0°C	17	
	Dry Bean Forage	< 0°C	19	
	Dry Bean Hay	< 0°C	16	
	Dry Bean Seed	< 0°C	16	
	Dry Pea Vines	< 0°C	18	
	Dry Pea Hay	< 0°C	18	
	Dry Pea Seed	< 0°C	17	
Penflufen	Soybean forage (Field Trial)	< 0°C	16	

Table 7.2 Summary of Storage Conditions and Durations for Penflufen Crop Field Trials

Residue	Matrix (RAC)	Storage Temperature (°C)	Actual Study Duration (months)	Limit of Demonstrated Storage Stability
	Soybean forage (Processing Study)	< 0°C	15	
	Soybean hay (Field Trial)	< 0°C	15	
	Soybean hay (Processing Study)	< 0°C	14	
	Soybean seed	< 0°C	13	
	Shelled Immature Seed (Processing Study)	< 0°C	13	
	Podded Immature Seed (Processing Study)	< 0°C	13	
	Mature Seed (Processing Study)	< 0°C	12	

[1] Storage stability data were provided for additional penflufen metabolites; however since those metabolites are not part of the residue of concern, those data are not included here.
[2] K+CWHR is kernel plus cob with husk removed.

Conclusions. Since the residue of concern for penflufen for both tolerance setting and risk assessment purposes is the parent compound, the conclusions here are limited to that analyte only. The submitted storage stability data were generated using a validated analytical method as discussed in Section 6.1.1. Adequate sample chromatograms and documentation of the laboratory portion of the study were provided. Acceptable recoveries were obtained in all matrices tested at the 26-27 month storage interval. Residues of penflufen are considered to be stable for at least 26 months in potato (tuber), lettuce (head), dry bean (seed), orange (fruit), wheat (grain and straw) and sunflower (seed) when stored frozen. Further, given the wide diversity of crops with demonstrated stability, the Agency concludes that residues in all matrices, including processed commodities are likely to be stable when stored frozen for up to 26 months.

8.0 Water, Fish, and Irrigated Crops (860.1400)

The proposed use on rice is limited to a seed treatment for dry-seeded rice. Given the application rate and planting of the treated seeds under the soil, it is unlikely that quantifiable residues of penflufen will occur in rice irrigation water (Chem SAC minutes 12/12/2007). Additionally, there are no direct aquatic applications of penflufen proposed; therefore, there are no issues associated with this guideline requirement related to these proposed new uses. However, should the registrant request an expansion of the use on rice, additional data on residues in water may be required.

9.0 Food Handling (860.1460)

There are no food handling establishment uses proposed in this submission; therefore a discussion of this guideline is not germane to this residue chemistry summary document.

10.0 Meat, Milk, Poultry, and Eggs (860.1480)

Feeding studies in livestock have not been submitted with this action; instead the petitioner has requested a waiver from the requirement to conduct these studies.

Conclusions. Based on the submitted data on the magnitude of the residue in plants, the Agency concludes that there not likely to be quantifiable residues of penflufen in the livestock feedstuffs associated with the newly proposed uses of this fungicide. Therefore, the Agency determines that these uses are classified as 180.6 (a) (3), no reasonable expectation of finite residues with respect to residues in livestock. The requested waiver is considered appropriate at this time and no feeding studies are required for penflufen. Further, tolerances for livestock commodities are not required. However, should the petitioner request uses in the future which result in measureable residues of penflufen in livestock feedstuffs, feeding studies and acceptable analytical methods may be required to support those uses.

11.0 Magnitude of the Residue

11.1 Food Residue Profile

The submitted data on the metabolism of penflufen in potatoes (seed treatment and in-furrow), wheat (seed treatment), soybeans (seed treatment) and rice (in soil at transplant) demonstrate that residues are generally low, but do translocate throughout the plants. The highest residues are generally found in the foliage or forage portions of plants (feedstuffs), and not in the tubers, seeds or grains of these commodities (food items). The registrant has provided studies on sunflower, cotton, canola, beans, peas and alfalfa that demonstrate there is no uptake of radioactivity into any aerial portion of those plants; indicating that penflufen is not taken up by these plants and that there is little likelihood of exposure to penflufen from consuming the edible portion of these commodities. Field trial data submitted for the remaining commodities showed no quantifiable residues of penflufen in any of the food or feedstuffs associated with those commodities.

11.2 Crop Field Trials (860.1500)

Appendix 3, U.S. EPA NAFTA GAP Study Summaries, October 2011

11.2.1 Alfalfa

Alfalfa TRR Study (MRID No. 48023648)

A study designed to trace total radioactive residues (TRR) of penflufen in alfalfa was submitted in lieu of alfalfa field trial data. Alfalfa seeds, treated with [pyrazole-3-^{14}C] penflufen at rates of 0.0035 lbs ai/100 lbs seed (3.5 mg ai/100 kg seed) and 0.0122 lbs ai/100 lbs seed (12.2 mg

ai/100 kg seed) were planted, grown to maturity and the alfalfa flowers, forage, and hay were harvested. Samples of alfalfa flowers, forage and hay were taken from three cuttings, homogenized and radioassayed. The average total radioactive residue (TRR) for each plant part is shown in the table below.

Table 11.2.1. Total Radioactive Residues in Alfalfa Flowers, Forage and Hay

Matrices	Cutting	Average TRR at low treatment rate[1](ppm)	Average TRR at high treatment rate[2] (ppm)
Flowers[3]	1st	<0.004 ppm	<0.004 ppm
	2nd	NA	NA
	3rd	<0.004 pm	<0.004 ppm
Forage[4]	1st	<0.003 ppm	<0.003 ppm
	2nd	<0.003 ppm	<0.003 ppm
	3rd	<0.003 ppm	<0.003 ppm
Hay[4]	1st	NA	NA
	2nd	<0.003 ppm	<0.003 ppm
	3rd	<0.003 ppm	<0.003 ppm

[1]Low treatment rate is equivalent to 3.46 g ai/100 kg seed.
[2]High treatment rate is equivalent to 12.23 g ai/100 kg seed.
[3]The LOD for flowers is 0.004 ppm.
[4]The LOD for hay and forage is 0.003 ppm.
NA = not collected and/or not analyzed.

Conclusions. The petitioner has provided TRR data labeled in only one ring. However, in reviewing the metabolism data for penflufen, while cleavage of the chemical is possible, the major degradation pathways seem to involve demethylation or conjugation with the backbone of the structure intact. In all metabolism studies and the confined rotational crop study, aniline or aniline related metabolites were not identified. Given that the only cleavage products identified in the metabolism studies where both rings were labeled were those involving the pyrazole ring, the Agency concludes that conducting the TRR studies with the pyrazole ring is sufficient to address the question of uptake.

Since residues in all aerial parts of the plant are below 0.005 ppm, and below the established method LOD, in accordance with the HED ChemSAC (Chemistry Science Advisory Committee) guidance on classification of seed treatments as food nonfood uses (10/28/99), the Agency would classify the seed treatment use of penflufen on alfalfa as a non-food use. No tolerances would be required to support this use; however, penflufen is being reviewed as part of a global review, and the registrant has requested tolerances in alfalfa hay and forage at 0.01 ppm. The Agency has no objection to establishing the requested tolerances since the TRR study clearly indicates that residues in alfalfa forage and hay will not exceed these tolerances.

11.2.2 Potato (Crop Subgroup 1C)

Potato Field Trials (MRID No. 48023729)

Twenty-six field trials (23 harvest and 3 decline) were conducted to measure the magnitude of penflufen residues in/on potatoes after two different treatment regimes: treatment of potato seed pieces at a target rate of 0.002 lb ai/100 lbs seed piece (2 g ai/100 kg seed piece), and treatment of potato seed pieces at a target rate of 0.002 lb ai/100 lbs seed piece followed by an in-furrow treatment of penflufen after planting for a maximum total treatment of 0.153 lb ai/A (170 g ai/ha).

Potato tubers were dug at earliest commercial harvest and allowed to dry according to normal practice before sampling. The location of the potato field trials is shown in Attachment 2, Table A3.1. Detailed use pattern information for the trials is provided in Table 6.3.6-6, Appendix 3.

Residues of penflufen and its metabolites, Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C were quantified by high performance liquid chromatography/triple stage quadrupole mass spectrometry (LC-MS/MS) using stable isotopically labelled internal standards (Method EL-002-P09-01). The method limit of quanitation (LOQ) was 0.01 ppm for each analyte in potato tubers.

Individual residues of penflufen, Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C were less than the LOQ (<0.01ppm) in all tuber samples. Detailed results from all field trials can be found in Table 6.3.6-8 of Appendix 3.

Individual Field Trial Conclusions. The North American potato field trials were generated using an adequate data collection method as discussed in Section 6.1 of this document. Adequate storage stability data are available as described in Section 7.0 of this summary document. The number and geographic representation are in accordance with OCSPP harmonized test guideline 860.1500. No additional field trial data for potato are required to support the requested use. Quantifiable residues of penflufen, the residue of concern for both risk assessment and tolerance setting purposes, are not likely in any potato raw agricultural commodity grown from treated seed.

Crop Subgroup Conclusions. The petitioner has provided field trial data for potato, the representative crop for crop subgroup 1C; therefore, a tolerance for this subgroup is adequately supported by residue data.

11.2.3 Legume Vegetables (Crop Group 6 and Crop Group 7)

Green Bean TRR Study (MRID No. 48023646)
A study designed to trace total radioactive residues (TRR) of penflufen in green beans was submitted in addition to field trial data (discussed below). Green bean seeds, treated with [pyrazole-3-^{14}C] penflufen at a rate of 0.0055 lbs ai/100 lbs seed (5.51 g ai/100 kg seed) were planted, grown to maturity and the bean pods and forage were harvested. Bean forage was not analyzed. The TRR in bean pods grown from treated seeds was <0.001 ppm, the method limit of detection (LOD).

Pea TRR Study (MRID No. 48023647)
A study designed to trace total radioactive residues (TRR) of penflufen in peas was submitted in addition to field trial data (discussed below). Pea seeds, treated with [pyrazole-3-^{14}C] penflufen at a rate of 0.0068 lbs ai/100 lbs seed (6.81 g ai/100 kg seed) were planted, grown to maturity and the succulent seed and forage were harvested. Pea forage was not analyzed. The average TRR in peas grown from treated seeds was <0.001 ppm, the method limit of detection (LOD).

Bean and Pea Field Trials (MRID No. 48023727)
Twenty residue trials were conducted, five on succulent pea, seven on dry pea, three on succulent bean and five on dry bean, to measure the magnitude of penflufen residues in/on succulent and dry peas and beans and the foliage of peas and beans following the planting of seeds treated with

penflufen at a rate of 0.005 lbs ai/100 lbs seed (5 g ai/100 kg seed). A control and a treated plot were used in each trial. In all trials, single control samples and duplicate treated samples of the legume commodities were collected from each plot at normal maturity. Hay and seed were allowed to dry to commercial dryness for 0 to 19 days prior to sampling. The location of the field trials is shown in Attachment 2, Table A3.2. Detailed use pattern information for the trials is provided in Table 6.3.3-6, Appendix 3.

Residues of penflufen and its metabolites, Pen-3HB, and Pen-HGT were quantified by high performance liquid chromatography/triple stage quadrupole mass spectrometry (LC-MS/MS) using stable isotopically labelled internal standards (Method EL-002-P09-01). The method limit of quanitation (LOQ) was 0.01 ppm for each analyte in all succulent and dry bean and pea matrices.

Individual residues of penflufen, Pen-3HB, and Pen-HGT were less than the LOQ (<0.01ppm) in all succulent and dry bean and pea commodities. Detailed results from all field trials can be found in Table 6.3.4-7 of Appendix 3.

Individual Field Trial Conclusions. The North American bean and pea field trials were generated using an adequate data collection method as discussed in Section 6.1 of this document. Adequate storage stability data are available as described in Section 7.0 of this summary document. The registrant has provided the number of field trials, reflecting the necessary geographic representation as agreed upon in discussions with the Agency (Chem SAC minutes 12/12/2007). This reduced data set is appropriate given the findings in the metabolism studies and TRR studies, the type of application (seed treatment) and the availability of data from both the U.S. and Canada. No additional field trial data for dry and succulent beans and peas are required to support the requested use. Quantifiable residues of penflufen, the residue of concern for both risk assessment and tolerance setting purposes, are not likely in any dry or succulent bean or pea raw agricultural commodity grown from treated seed.

Soybean Field Trials (MRID No. 48023728)

Field trials were conducted at seven locations to measure the magnitude of penflufen residues in soybean seed, forage and hay following the planting of seeds treated with penflufen at a rate of 0.005 lbs ai/100 lbs seed (5 g ai/100 kg seed). A control and a treated plot were used in each trial. In all trials, single control samples and duplicate treated samples of the soybean commodities were collected from each plot at normal maturity. The location of the field trials is shown in Attachment 2, Table A3.3. Detailed use pattern information for the trials is provided in Table 6.3.5-6, Appendix 3.

Residues of penflufen and its metabolites, Pen-3HB, and Pen-HGT were quantified by high performance liquid chromatography/triple stage quadrupole mass spectrometry (LC-MS/MS) using stable isotopically labelled internal standards (Method EL-002-P09-01). The method limit of quanitation (LOQ) was 0.01 ppm for each analyte in all soybean matrices.

Individual residues of penflufen, Pen-3HB, and Pen-HGT were less than the LOQ (<0.01ppm) in all soybean commodities. Detailed results from all field trials can be found in Table 6.3.5-7 of Appendix 3.

Individual Field Trial Conclusions. The North American soybean field trials were generated using an adequate data collection method as discussed in Section 6.1 of this document. Adequate storage stability data are available as described in Section 7.0 of this summary document. The registrant has provided the number of field trials, reflecting the necessary geographic representation as agreed upon in discussions with the Agency (Chem SAC minutes 12/12/2007). This reduced data set is appropriate given the findings in the metabolism studies, the type of application (seed treatment) and the availability of data from both the U.S. and Canada. No additional field trial data for soybeans are required to support the requested use. Since the proposed use is a pre-harvest use of penflufen and residues above the LOQ are not found in grain, residue data and a tolerance for aspirated grain fractions is not required to support the requested use on soybeans. Quantifiable residues of penflufen, the residue of concern for both risk assessment and tolerance setting purposes, are not likely in any soybean raw agricultural commodity grown from treated seed.

Crop Group Conclusions. The petitioner has provided field trial data for dry and succulent beans and peas and soybeans. An adequate number of field trials have been received for all the representative crops in the crop group. Residues in all commodities in this group are less than the method LOQ of 0.01 ppm in all matrices; therefore the submitted field trial data support a crop group tolerance for legume vegetables (Crop Group 6) and a tolerance for the foliage of legume vegetables (Crop Group 7).

11.2.4 Cereal Grains (Crop Group 15 and Crop Group 16)

Wheat Field Trials (MRID No. 48023724)

Field trials were conducted at nine locations to measure the magnitude of penflufen residues in/on the wheat commodities of forage, hay, grain, and straw following the planting of seeds treated with penflufen at a rate of 0.005 lb ai/100 lbs seed (5 g ai/100 kg seed). A control and a treated plot were used in each trial. In all trials, single control samples and duplicate treated samples of the wheat commodities were collected from each plot at normal maturity. Hay was allowed to dry to commercial dryness prior to sampling. The location of the wheat field trials is shown in Attachment 2, Table A3.4. Detailed use pattern information for the trials is provided in Table 6.3.1-6, Appendix 3.

Residues of penflufen and its metabolites, Pen-3HB, and Pen-HGT were quantified by high performance liquid chromatography/triple stage quadrupole mass spectrometry (LC-MS/MS) using stable isotopically labelled internal standards (Method EL-002-P09-01). The method limit of quanitation (LOQ) was 0.01 ppm for each analyte in all wheat matrices.

Individual residues of penflufen, Pen-3HB, and Pen-HGT were less than the LOQ (<0.01ppm) in all wheat commodities. Detailed results from all field trials can be found in Table 6.3.1-7 of Appendix 3.

Individual Field Trial Conclusions. The North American wheat field trials were generated using an adequate data collection method as discussed in Section 6.1 of this document. Adequate storage stability data are available as described in Section 7.0 of this summary document. The registrant has provided the number of field trials, reflecting the necessary geographic

representation as agreed upon in discussions with the Agency (Chem SAC minutes 12/12/2007). This reduced data set is appropriate given the findings in the metabolism studies, the type of application (seed treatment) and the availability of data from both the U.S. and Canada. No additional field trial data for wheat are required to support the requested use. Quantifiable residues of penflufen, the residue of concern for both risk assessment and tolerance setting purposes, are not likely in any wheat raw agricultural commodity grown from treated seed.

Barley Field Trials (MRID No. 48023725)

Field trials were conducted at twelve locations to measure the magnitude of penflufen residues in/on barley grain, hay and straw following the planting of seeds treated with penflufen at a rate of 0.005 lbs ai/100 lbs of seed. A control and a treated plot were used in each trial. In all trials, single control samples and duplicate treated samples of the barley commodities were collected from each plot at normal maturity. Hay was allowed to dry to commercial dryness prior to sampling. The location of the barley field trials is shown in Attachment 2, Table A3.5. Detailed use pattern information for the trials is provided in Table 6.3.2-6, Appendix 3.

Residues of penflufen and its metabolites, Pen-3HB, and Pen-HGT were quantified by high performance liquid chromatography/triple stage quadrupole mass spectrometry (LC-MS/MS) using stable isotopically labelled internal standards (Method EL-002-P09-01). The method limit of quanitation (LOQ) was 0.01 ppm for each analyte in all barley matrices.

Individual residues of penflufen, Pen-3HB and Pen-HGT were less than the LOQ (<0.01ppm) on all barley matrices (hay, grain and straw). Detailed results from all field trials can be found in Table 6.3.2-7 of Appendix 3.

Individual Field Trial Conclusions. The North American barley field trials were generated using an adequate data collection method as discussed in Section 6.1 of this document. Adequate storage stability data are available as described in Section 7.0 of this summary document. No U.S. field trial data were provided for barley. This is consistent with the agreement in discussions between the Agency and the registrant (Chem SAC minutes 12/12/2007). U.S. barley field trials were not required given the findings in the metabolism studies, the available U.S. wheat data, the type of application (seed treatment) and the availability of data from Canada. No field trial data for barley are required to support the requested use. Quantifiable residues of penflufen, the residue of concern for both risk assessment and tolerance setting purposes, are not likely in any barley raw agricultural commodity grown from treated seed.

Corn Field Trials (MRID No. 48023726)

Field trials were conducted at nine locations to measure the magnitude of penflufen residues in/on sweet corn ears and forage (target maturity BBCH 73), field corn forage (target maturity BBCH 85), corn grain, and corn stover (target maturity BBCH 89) following the planting of seeds treated with penflufen at a rate of 0.01 lb ai/100 lbs seed (10 g ai/100 kg seed). A control and a treated plot were used in each trial. In all trials, single control samples and duplicate treated samples of the corn commodities were collected from each plot at normal maturity. The location of the corn field trials is shown in Attachment 2, Table A3.6. Detailed use pattern information for the trials is provided in Table 6.3.3-6, Appendix 3.

Residues of penflufen and its metabolites, Pen-3HB, and Pen-HGT were quantified by high performance liquid chromatography/triple stage quadrupole mass spectrometry (LC-MS/MS) using stable isotopically labelled internal standards (Method EL-002-P09-01). The method limit of quantitation (LOQ) was 0.01 ppm for each analyte in all corn matrices.

Individual residues of penflufen and its metabolites, Pen-3HB and Pen-HGT, were less than the LOQ (<0.01 ppm) in all of the corn matrices (sweet corn forage, sweet corn K+CWHR, field corn forage, field corn grain and stover/fodder).

Individual Field Trial Conclusions. The North American corn field trials were generated using an adequate data collection method as discussed in Section 6.1 of this document. Adequate storage stability data are available as described in Section 7.0 of this summary document. The registrant has provided the number of field trials, reflecting the necessary geographic representation as agreed upon in discussions with the Agency (Chem SAC minutes 12/12/2007). This reduced data set is appropriate given the findings in the metabolism studies, the type of application (seed treatment) and the availability of data from both the U.S. and Canada. No additional field trial data for corn are required to support the requested use. Quantifiable residues of penflufen, the residue of concern for both risk assessment and tolerance setting purposes, are not likely in any corn raw agricultural commodity grown from treated seed.

Rice

Field trial data were not submitted for rice. However, since the registrant has requested use on rice as a seed treatment only to dry-seeded rice, the Agency will translate information in the submitted rice metabolism study to support the newly proposed use on rice. The rice metabolism study (MRID 48023640) is summarized in Section 5.1 of this review and a detailed review is included in Appendix 1.

Individual Commodity Conclusions. In the metabolism study, rice plants received a soil treatment at transplant of 0.45 lbs ai/A. The requested use is for 0.005 lbs ai/100 lbs seed. Since the metabolism study reflects a significantly higher application rate than is currently proposed, and a slightly later planting interval and residues were extremely low in the rice kernel, the Agency concludes that residues in rice grain grown from treated seed are not likely to exceed 0.01 ppm, the LOQ for the proposed enforcement method. No additional data are required to support the requested use as a seed treatment in dry-seeded rice, however, if any expansion of the use on rice is requested, additional field trial data may be required.

Crop Group Conclusions. The petitioner has provided field trial data for wheat, barley, corn and metabolism data for rice. No data have been provided on aspirated grain fractions for any cereal grain; however based on the proposed use pattern and the lack of quantifiable residues in cereal grains, residue data and a tolerance for aspirated grain fractions is not required to support the requested use of penflufen on cereal grains. An adequate number of field trials have been received for all the representative crops in the crop group. Residues in all commodities in this group are less than the method LOQ of 0.01 ppm in all matrices; therefore the submitted field trial data support a crop group tolerance for the cereal grains (Crop Group 15) and the forage, fodder and straw of cereal grains (Crop Group 16). The petitioner is advised that since field trial data for rice have not been provided, the metabolism data at transplant will be translated to use as a seed

treatment in dry seeded rice only. Should the registrant wish to expand the use on rice beyond this limited use pattern, additional data may be required.

11.2.4 Oil Seeds (Crop Group 20)

Sunflower TRR Study (MRID No. 48023642)
A study designed to trace total radioactive residues (TRR) of penflufen in sunflower was submitted in lieu of field trial data. Sunflower seed, treated with [pyrazole-3-^{14}C]BYF 14182 at a rate of 0.0186 lb ai/100 lbs seed (18.56 g ai/100 kg seed), was planted, grown to maturity and the seed from mature sunflowers was harvested. The sunflower seed was homogenized and radioassayed. The TRR in mature sunflower seed was <0.0016 ppm, the method LOD, in all samples.

Cotton TRR Study (MRID No. 48023644)
A study designed to trace total radioactive residues (TRR) of penflufen in cotton was submitted in lieu of field trial data. Cotton seed, treated with [pyrazole-3-^{14}C] BYF 14182 at a rate of 10.7 g active ingredient (ai)/100 kg seed, was planted, and cotton was grown to maturity. Seed cotton and cotton gin byproducts (gin trash) were collected from the mature cotton. Seed cotton was hand-ginned to generate undelinted cottonseed. The undelinted cottonseed and cotton gin byproducts were homogenized and radioassayed. The TRR in undelinted cottonseed and cotton gin byproducts was <0.0012 ppm, the method LOD, in all samples.

Canola TRR Study (MRID No. 48023645)
A study designed to trace total radioactive residues (TRR) of penfluen in canola was submitted in lieu of field trial data. Canola seed, treated with [pyrazole-3-^{14}C] BYF 14182 at a rate of 15.65 g active ingredient (ai)/100 kg seed, was planted, and the canola was grown to maturity. The canola was harvested at maturity, the seeds were collected, homogenized and radioassayed. The TRR in the mature canola seed was <0.00064 ppm, the method LOD, in all samples.

Conclusions. The petitioner has provided TRR data labeled in only one ring. However, in reviewing the metabolism data for penflufen, while cleavage of the chemical is possible, the major degradation pathways seem to involve demethylation or conjugation with the backbone of the structure intact. In all metabolism studies and the confined rotational crop study, aniline or aniline related metabolites were not identified. Given that the only cleavage products identified in the metabolism studies where both rings were labeled were those involving the pyrazole ring, the Agency concludes that conducting the TRR studies with the pyrazole ring is sufficient to address the question of uptake in oilseeds.

Since residues in all aerial parts of the plant are below 0.005 ppm, and below the established method LOD, in accordance with the HED ChemSAC (Chemistry Science Advisory Committee) guidance on classification of seed treatments as food nonfood uses (10/28/99), the Agency would classify the seed treatment use of penflufen on sunflower, cotton and canola, the representative commodities in the oilseed crop group, to be non-food uses. Further since all representative crops are non-food, the Agency would consider seed treatment application of penflufen to all oilseeds to be non-food uses. No tolerances would be required to support these uses; however, penflufen is being reviewed as part of a global review, and the registrant has requested tolerances

for the oilseeds crop group 20 and cotton gin byproducts, both at 0.01 ppm. The Agency has no objection to establishing the requested tolerances since the TRR study clearly indicates that residues in oil seeds and gin byproducts will not exceed these tolerances.

11.3 Processed Food and Feed (860.1520)

Appendix 3, U.S. EPA NAFTA GAP Study Summaries, October 2011

11.3.1 Potato Processing Study (MRID No. 48023737)

Bayer CropScience has conducted a processing study to address the potential for residues of penflufen and its metabolites, Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C to concentrate in processed potato commodities. To provide potato samples for the study, an exaggerated rate potato field trial was conducted in the United States in 2008. Potatoes were grown from potato seed pieces that had been treated with penflufen at a rate of 0.010 lbs ai/100 lbs, followed by an in-furrow application of penflufen at 0.469 lb ai/A (approximately 5X the proposed in-furrow rate). Potato tubers were processed into potato wet peel, potato flakes and potato chips simulating as closely as possible commercial practices. Residues of penflufen were quantitated by liquid chromatography/tandem mass spectrometry (LC-MS/MS) using isotopically labeled internal standards (Method EL-002-P09-01). The method LOQ is 0.01 ppm for each analyte.

All residues of penflufen and its metabolite, Pen -3HB were less than the LOQ (<0.01 ppm) in potato tubers, but were above the method limit of detection (LOD). Residues of Pen-HGT, Pen-PCX and Pen-D3C were not detectable in potato tubers (<LOD) and all processed commodities. Quantifiable residues of penflufen (average 0.0338 ppm) were seen in potato wet peel. Residues of penflufen in flakes and chips were <LOD. Residues of Pen-3HB below the LOQ, but above the LOD were seen in all processed commodities. The residue data and calculated processing factors are summarized in the table below.

Table 11.31.1 Residue Data from the Potato Processing Study with Penflufen.

RAC[1]	Processed Commodity	Total Rate lb ai/A (g ai/ha)	PHI (day)	Residues (ppm)	Processing Factor
				Penflufen	Penflufen
Potato Replicate 1	Potato Tuber	0.01 lbs ai/A100 lbs seed plus 0.469 lb ai/A in furrow	NS[2]	0.0077	-
	Potato Wet Peel			0.0318	4.13
	Potato Flakes			ND[3]	-
	Potato Chips			ND	-
Potato Replicate 2	Potato Tuber	0.01 lbs ai/A100 lbs seed plus 0.469 lb ai/A in furrow	NS[1]	0.0088	-
	Potato Wet Peel			0.0278	3.16
	Potato Flakes			ND	-
	Potato Chips				-
Potato Replicate 3	Potato Tuber	0.01 lbs ai/A100 lbs seed plus 0.469 lb ai/A in furrow	NS	0.0078	-
	Potato Wet Peel			0.0419	5.37
	Potato Flakes			ND	-
	Potato Chips			ND	-
			Average Processing Factors	**Potato Wet Peel**	**4.22**
				Potato Flakes	**-**
				Potato Chips	**-**

[1] RAC is "raw agricultural commodity".
[2] NS is "not specified" – seed treatment and in-furrow uses on potatoes.

[3] ND is "not detected"; less than the method LOD of 0.003 ppm.

Conclusions. The submitted processing study reflected as closely as possible commercial processing of potatoes treated with exaggerated rates of penflufen. The residue data were generated using a validated data collection method as discussed in Section 6.1 of this document. Adequate storage stability data are available as discussed in Section 7.0 of this document. Adequate documentation of the study has been provided.

The processed commodities for potatoes include granules/flakes, chips, and wet peel. Since the residue of concern for penflufen is parent compound only, conclusions are limited to penflufen only. The Agency concludes that residues of the parent compound do not appear to concentrate in potato flakes or chips, but may concentrate in wet potato peel at up to 4.22X. While residues of penflufen do appear to concentrate in wet potato peel, the residue data in the table above reflect a 5X exaggerated application rate; if the residues are corrected to reflect the requested application rate, residues in wet peel will be less than 0.01 ppm, the method LOQ and the recommended tolerance for potatoes. Since the wet peel residue is not likely to exceed the established tolerance for the RAC, a separate tolerance for wet peel is not required.

An acceptable potato processing study has been submitted. No additional data with respect to concentration in potato processed commodities are required to support the proposed seed piece and in-furrow uses.

11.3.2 Soybean Processing Study (MRID No. 48023736)

To address the need for a soybean processing study, Bayer CropScience conducted three soybean exaggerated rate field trials in the U.S. in 2008. Soybeans were grown from seed treated with penflufen at 0.025 lbs ai/100 lbs seed (25 g ai/100 kg seed), 5X the currently proposed seed treatment application rate. Residues of penflufen, Pen-3HB and Pen-HGT were quantitated by liquid chromatography/tandem mass spectrometry (LC-MS/MS) using isotopically labeled internal standards (Method EL-002-P09-01). The method LOQ is 0.01 ppm for each analyte.

No quantifiable residues of penflufen or its metabolites, Pen-3HB and Pen-HGT, were observed in shelled immature seed, podded immature seed, mature seed, or hay samples. There were no quantifiable residues of penflufen or Pen-HGT in forage. There were no quantifiable residues of Pen-3HB in forage in two of the three trials and the residues found in the forage in the third trial were just above the method LOQ of 0.01 ppm.

Conclusions. The exaggerated rate field trial data were generated using a validated data collection method as discussed in Section 6.1 of this document. Adequate storage stability data to support this study are available as discussed in Section 7.0 of this document. Adequate documentation of the study has been provided.

The processed commodities for soybeans include meal, hulls and refined oil, all derived from the seed. Since the residue of concern for penflufen is parent compound, conclusions are limited to penflufen only. Quantifiable residues of penflufen were not seen in soybean seed grown from seed treated at 5X the proposed application rate. Therefore, the Agency concludes that

quantifiable residues of the parent compound are not likely in soybean processed commodities derived from soybean grown from treated seed at the currently requested application rate.

The requirement for information to address the potential for concentration in processed commodities has been satisfied. No additional data with respect to residues in soybean processed commodities are required to support the proposed seed treatment use.

11.3.3 Wheat Processing Study (MRID No. 48023735)

To address the need for a wheat processing study, Bayer CropScience conducted three wheat exaggerated rate field trials in Canada in 2008. Wheat was grown from seeds treated with penflufen at 0.025 lbs ai/100 lbs seed (25 g ai/100 kg seed), 5X the currently proposed seed treatment application rate. Residues of penflufen, Pen-3HB and Pen-HGT were quantitated by liquid chromatography/tandem mass spectrometry (LC-MS/MS) using isotopically labeled internal standards (Method EL-002-P09-01). The method LOQ is 0.01 ppm for each analyte.

No quantifiable residues of penflufen or its metabolites, Pen-3HB and Pen-HGT, were observed in wheat grain, hay or straw grown from seed treated with penflufen at a 5X application rate. There were no quantifiable residues of penflufen or Pen-HGT in forage. There were no quantifiable residues of Pen-3HB in two of the three field trials, and the residues observed in the third trial (0.020, 0.025) were only slightly above the method LOQ of 0.01 ppm.

Conclusions. The exaggerated rate field trial data were generated using a validated data collection method as discussed in Section 6.1 of this document. Adequate storage stability data to support this study are available as discussed in Section 7.0 of this document. Adequate documentation of the study has been provided.

The processed commodities for wheat include bran, flour, middlings, shorts and germ, all commodities processed from wheat grain. Since the residue of concern for penflufen is parent compound, conclusions are limited to penflufen only. Quantifiable residues of penflufen were not seen in wheat grain grown from seed treated at 5X the proposed application rate. Therefore, the Agency concludes that quantifiable residues of the parent compound are not likely in wheat processed commodities derived from wheat grown from treated seed at the currently requested application rate.

The requirement for information to address the potential for concentration in processed commodities has been satisfied. No additional data with respect to residues in wheat processed commodities are required to support the proposed seed treatment use.

11.3.4 Corn Processing Study (MRID No.48023734)

To address the need for a corn processing study, Bayer CropScience conducted an exaggerated corn field trial in Canada in 2008. Corn was grown from seeds treated with penflufen at 0.050 lbs ai/100 lbs seed (50 g ai/100 kg seed), 5X the currently proposed seed treatment application rate. Residues of penflufen, Pen-3HB and Pen-HGT were quantitated by liquid chromatography/tandem mass spectrometry (LC-MS/MS) using isotopically labeled internal

standards (Method EL-002-P09-01). The method LOQ is 0.01 ppm for each analyte.

No quantifiable residues of penflufen or its metabolites, Pen-3HB and Pen-HGT, were observed in corn grain grown from seed treated with penflufen at a 5X exaggerated rate.

Conclusions. The exaggerated rate field trial data were generated using a validated data collection method as discussed in Section 6.1 of this document. Adequate storage stability data to support this study are available as discussed in Section 7.0 of this document. Adequate documentation of the study has been provided.

The processed commodities for corn are from use on field corn and include refined oil from wet milling and meal and refined oil from dry milling. Since the residue of concern for penflufen is parent compound, conclusions are limited to penflufen only. Quantifiable residues of penflufen were not seen in corn grain grown from seed treated at 5X the proposed application rate. Therefore, the Agency concludes that quantifiable residues of the parent compound are not likely in corn processed commodities derived from corn grown from treated seed at the currently requested application rate.

The requirement for information to address the potential for concentration in processed commodities has been satisfied. No additional data with respect to residues in corn processed commodities are required to support the proposed seed treatment use.

11.4 Field Accumulation in Rotational Crops (860.1900)

Appendix 3, U.S. EPA NAFTA GAP Study Summaries, October 2011

Eighteen field rotational crop trials (MRID No. 48023741), six wheat, six turnip, and six mustard green trials were conducted in North America in 2008 to measure the magnitude of penflufen residues in rotational crops. The crops were planted at three plant-back intervals (1, 6 or 12-month PBIs) following a primary crop of potatoes grown from either treated seed pieces (0.002 lb ai/100 lb seed)or treated seed pieces (0.002 lb ai/100 lb seed) and in-furrow treatment (0.066lb ai/A). Seeds were sown at a rate of 4000 kg seed/ha for an application rate of 80 g ai/ha (0.071 lb ai/A) for the treated seeds or 160 g ai/ha (0.142 lb ai/A) for the combined treated seed pieces and in-furrow application.

Residues of penflufen and its metabolites Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C were quantitated by high pressure liquid chromatography/triple stage quadrupole mass spectrometry (LC/MS/MS) using the stable isotopically labeled analog of each analyte as an internal standard using analytical method EL-003-P09-01. The limit of quantitation (LOQ) was 0.01 ppm for each analyte in all matrices.

In wheat, no residues of penflufen or its metabolites greater than the LOQ (0.01 ppm) were observed in wheat grain at any PBI for either treatment regime. Further, no residues of penflufen, Pen-HGT, Pen-PCX, or PenD3C were observed in any wheat matrices. Very low levels (<0.05 ppm) of Pen-3HB were detected in a few samples of wheat forage and hay and no residues of Pen-3HB greater than 0.01 ppm were seen in straw at either rate.

Residues of penflufen, Pen-HGT, Pen-PCX and Pen-D3C were all <0.01 ppm, the method LOQ in mustard greens. Pen-3HB was seen in a few field trials at low levels (≤0.05 ppm) and in one trial at <0.2 ppm, with most trials having residues of Pen-3HB of <0.01 ppm.

In turnip tops, residues of penflufen, Pen-HGT, Pen-PCX and Pen-D3C were all <0.01 ppm. A few top samples had residues of Pen-3HB at low levels (<0.05 ppm), with most trials having residues of Pen-3HB in tops at <0.01ppm. No quanitifiable residues of penflufen, Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C were found in turnip roots.

Conclusions. The limited field trial data were generated using a validated analytical method and are supported by adequate storage stability data. In accordance with OCSPP 860.1900 guidance, limited field trials were conducted in a root and tuber vegetable (turnips), leafy vegetable (mustard greens) and small grain (wheat). The ROCKS committee has determined that the residue of concern in rotational crops is parent only (see Section 5.4, above). No residues of concern were identified in any of the rotational crops at a 30-day plant back interval; therefore, tolerances in rotational crops are not required. Further, since residues above the LOQ were not observed at the 30-day PBI, rotational crop restrictions are not required.

The requirements for limited field trials have been adequately addressed for these seed treatment/in-furrow uses. However, the registrant is advised that if new uses are proposed which would result in significantly higher soil loading, additional field rotational crop data may be required.

12.0 Recommended Tolerances (860.1550)

Since there are no quantifiable residues in the food and feedstuffs that are the subject of this petition, recommended tolerances are set at the analytical method limit of quantitation (LOQ) of 0.01 ppm. See Section 2.2.3 for the recommended tolerance expression and tolerance summary table for penflufen. Section 2.2.4 provides a discussion of revisions to the petitioner's recommended tolerances and Section 2.2.2 discusses international harmonization.

13.0 Attachments

Attachment 1. Penflufen Metabolite Structures
Attachment 2. Field Trial Geographic Distribution

Appendix 1. Penflufen – Core Metabolism and Storage Stability Studies, APVMA Review
Appendix 2. Penflufen – Analytical Methods, APVMA Review
Appendix 3. Penflufen – NAFTA GAP Studies, U.S. EPA Review
Appendix 4. Penflufen – Final Storage Stability Study, APVMA Review

Attachment 1. Penflufen Metabolite Structures

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

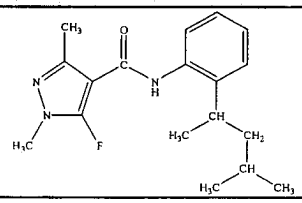
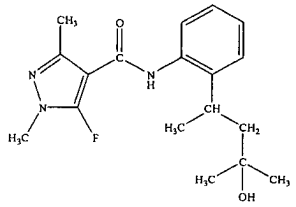
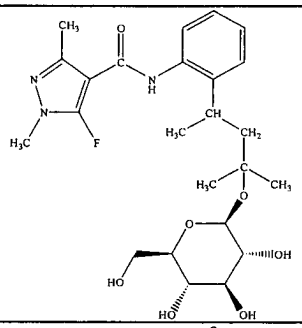
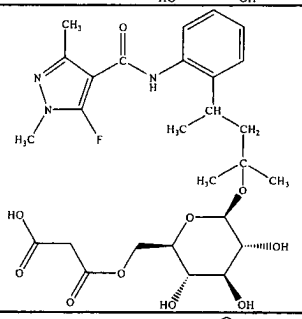
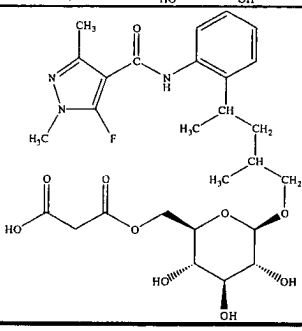
Common Names / Code	IUPAC Name	Chemical Structure
Penflufen BYF 14182	N-[2-(1,3-Dimethylbutyl)phenyl] 5-fluoro-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-3-hydroxy-butyl Pen-3HB BCS-AA10006	5-fluoro-N-[2-(3-hydroxy-1,3-dimethylbutyl)phenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-3-hydroxy-butyl-glucoside BCS-AA10006-glucoside	5-fluoro-N-{2-[3-(beta-D-glucopyranosyloxy)-1,3-dimethylbutyl]phenyl}-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-3-hydroxy-butyl-malonyl-glucoside BCS-AA10006-malonyl-glucoside	3-(2-{[(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl)-1,1-dimethylbutyl 6-O-(carboxyacetyl)-beta-D-glucopyranoside	
BYF 14182-4-hydroxy-butyl-malonyl-glucoside	4-(2-{[(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl)-2-methylpentyl 6-O-(carboxyacetyl)-beta-D-glucopyranoside	

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

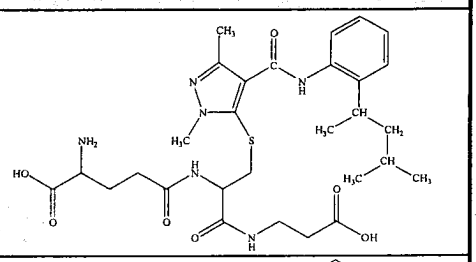
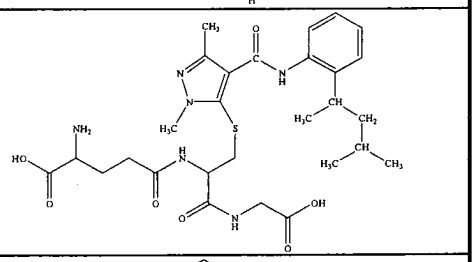
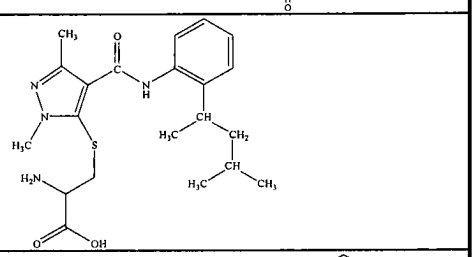
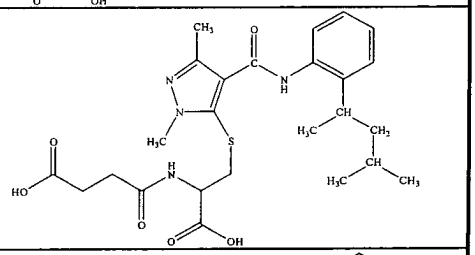
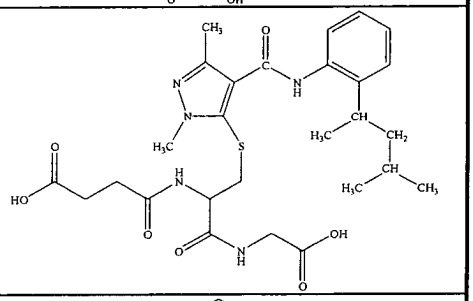
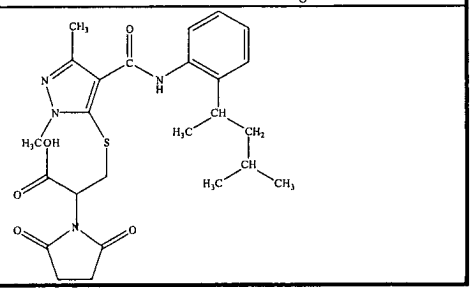
Common Names / Code	IUPAC Name	Chemical Structure
BYF 14182-homoglutathione Pen-HGT BCS-AA10790	Gamma-glutamyl-S-(4-{[2-(1,3-dimethylbutyl)phenyl]carbamoyl}-1,3-dimethyl-1H-pyrazol-5-yl)cysteinyl-beta-alanine	
BYF 14182-glutathione	gamma-glutamyl-S-(4-{[2-(1,3-dimethylbutyl)phenyl]carbamoyl}-1,3-dimethyl-1H-pyrazol-5-yl)cysteinyl-glycine	
BYF 14182-cysteine	S-(4-{[2-(1,3-dimethylbutyl)phenyl]carbamoyl}-1,3-dimethyl-1H-pyrazol-5-yl)cysteine	
BYF 14182-succinyl-cysteine	4-({1-carboxy-2-[(4-{[2-(1,3-dimethylbutyl)phenyl]carbamoyl}-1,3-dimethyl-1H-pyrazol-5-yl)thio]ethyl}amino)-4-oxobutanoic acid	
BYF 14182-succinyl-cysteinyl-glycine	N-(3-carboxypropanoyl)-S-(1,3-dimethyl-4-{[2-(4-methylpentan-2-yl)phenyl]carbamoyl}-1H-pyrazol-5-yl)cysteinylglycine	
BYF 14182-cysteinyl succinimide	3-[(1,3-dimethyl-4-{[2-(4-methylpentan-2-yl)phenyl]carbamoyl}-1H-pyrazol-5-yl)sulfanyl]-2-(2,5-dioxopyrrolidin-1-yl)propanoic acid	

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

Common Names / Code	IUPAC Name	Chemical Structure
BYF 14182-sulfonic acid	1,3-dimethyl-4-{[2-(4-methylpentan-2-yl)phenyl]carbamoyl}-1H-pyrazole-5-sulfonic acid	
BYF 14182-hydroxy-sulfonic acid	Structure not specified	
BYF 14182-hydroxy-acetyl-cysteine	Structure not specified	
BYF 14182-pyrazole-4-carboxamide Pen-PCX BCS-AA10791	5-Fluoro-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-bis–desmethyl-3-carboxylic acid Pen-D3C BCS-CM41431	5-Fluoro-1H-pyrazole-3-carboxylic acid	
BYF 14182-hydroxy-mercapto-lactic acid	Structure not specified	

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

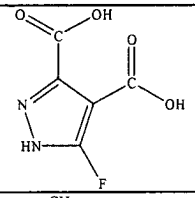
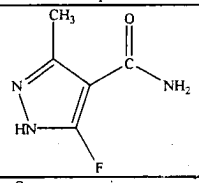
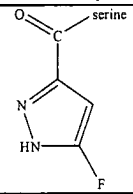
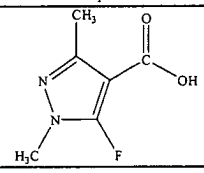
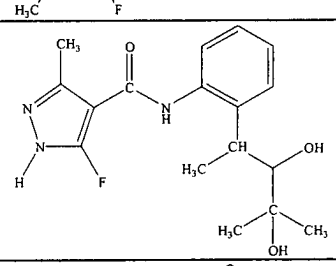
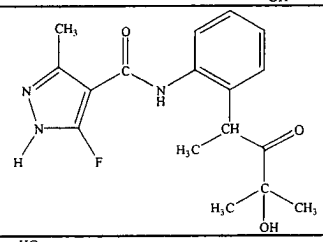
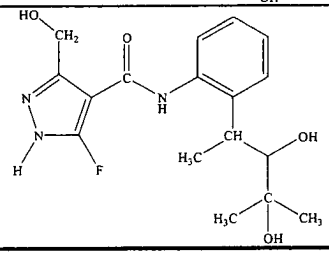
Common Names / Code	IUPAC Name	Chemical Structure
BYF 14182-desmethyl-dicarboxylic acid	5-fluoro-1H-pyrazole-3,4-dicarboxylic acid	
BYF 14182-desmethyl-pyrazole-4-carboxamide	5-fluoro-3-methyl-1H-pyrazole-4-carboxamide	
BYF 14182-bis-desmethyl-3-carbonyl-serine	Structure not completely specified	
BYF 14182 – fluoro acid	5-fluoro-1,3-dimethyl-1H-pyrazole-4- carboxylic acid	
BYF 14182-desmethyl-2,3-dihydroxy	N-[2-(2,3-dihydroxy-1,3-dimethylbutyl)phenyl]-5-fluoro-3-methyl-1H-pyrazole-4-carboxamide	
BYF 14182-desmethyl-3-hydroxy-ketone	5-fluoro-N-[2-(3-hydroxy-1,3-dimethyl-2-oxobutyl)phenyl]-3-methyl-1H-pyrazole-4-carboxamide	
BYF 14182-desmethyl-hydroxymethyl-2,3-dihydroxy	N-[2-(2,3-dihydroxy-1,3-dimethylbutyl)phenyl]-5-fluoro-3-(hydroxymethyl)-1H-pyrazole-4-carboxamide	

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

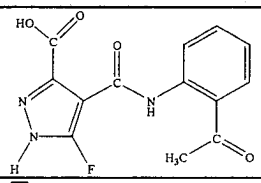
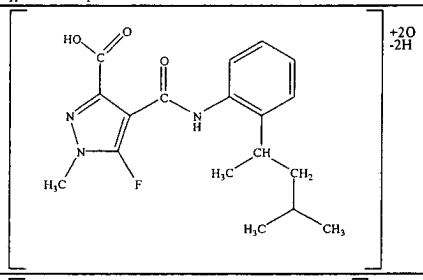
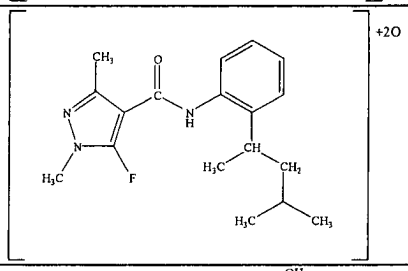
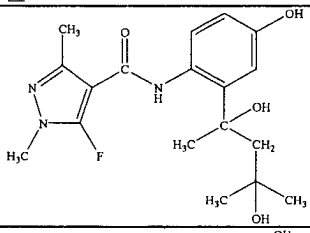
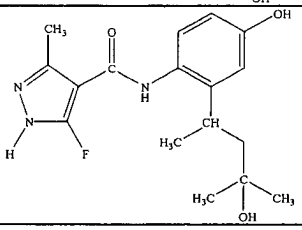
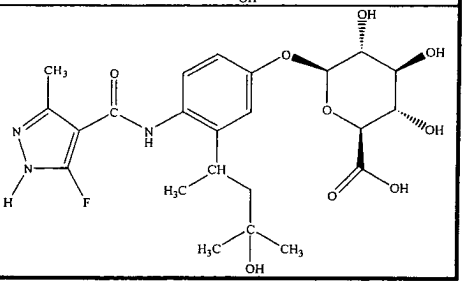
Common Names / Code	IUPAC Name	Chemical Structure
BYF 14182-desmethyl-acetyl-carboxylic acid	4-[(2-acetylphenyl)carbamoyl]-5-fluoro-1H-pyrazole-3-carboxylic acid	
BYF 14182-hydroxy-keto-carboxylic acid	Structure not completely specified	
BYF 14182-dihydroxy (isomer 1 and 2)	Structure not completely specified	
BYF 14182-1,3,4'-trihydroxy	N-[2-(1,3-dihydroxy-1,3-dimethylbutyl)-4-hydroxyphenyl]-5-fluoro-1,3-dimethyl)-1H-pyrazole-4-carboxamide	
BYF 14182-3,4'-dihydroxy	5-fluoro-N-[4-hydroxy-2-(3-hydroxy-1,3-dimethylbutyl)phenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-3,4'-dihydroxy-glucuronide	4-{[(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)carbonyl]amino}-3-(4-hydroxy-4-methylpentan-2-yl)phenyl beta-D-glucopyranosiduronic acid	

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

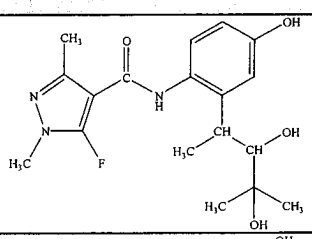
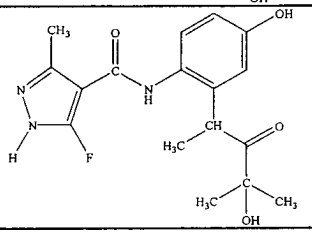
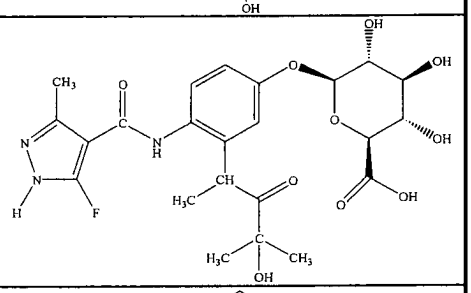
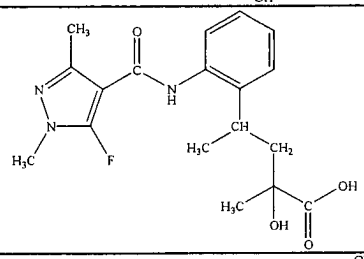
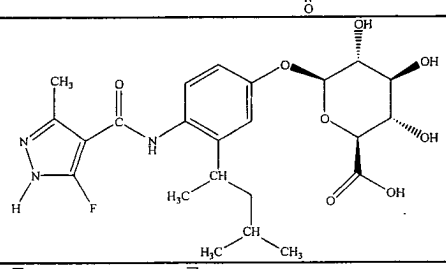
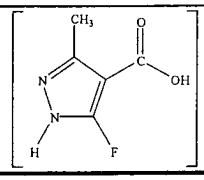
Common Names / Code	IUPAC Name	Chemical Structure
BYF 14182-2,3,4'-trihydroxy	N-[2-(2,3-dihydroxy-1,3-dimethylbutyl)-4-hydroxyphenyl]-5-fluoro-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-3,4'-dihydroxy-ketone	5-fluoro-N-[4-hydroxy-2-(3-hydroxy-1,3-dimethyl-2-oxobutyl)phenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-3,4'-dihydroxy-keto-glucuronide	4-{[(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)carbonyl]amino}-3-(3-hydroxy-1,3-dimethyl-2-oxobutyl)phenyl beta-D-glucopyranosiduronic acid	
BYF 14182-3-hydroxy-pentanoic acid	4-(2-{[(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl-2-hydroxy-2-methylpentanoic acid	
BYF 14182-4'-hydroxy – glucuronide (isomer 1 and 2)	3-(1,3-dimethylbutyl)-4-{[(5-fluoro-1,3,dimethyl-1H-pyrazol-4-yl)carbonyl]amino}phenylbeta-D-glucopyranosiduronic acid	
BYF 14182-desmethyl-4-carboxylic acid-glucuronide	Structure not completely specified	 + glucuronic acid

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

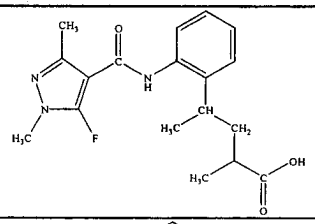
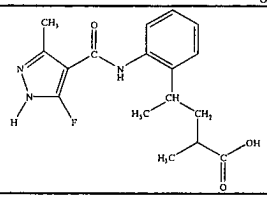
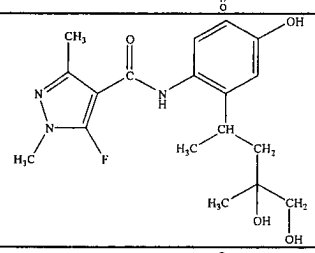
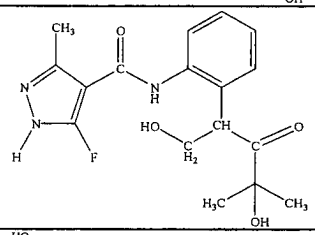
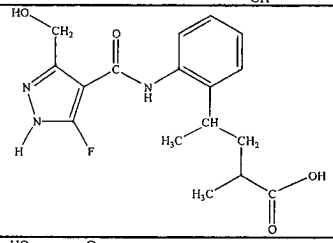
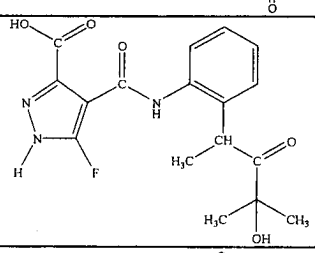
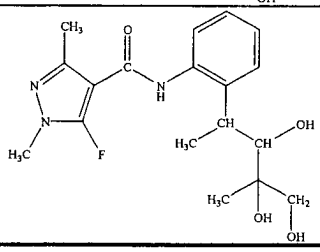
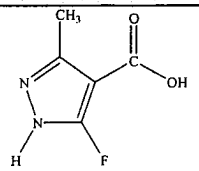
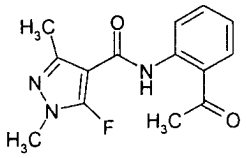
Common Names / Code	IUPAC Name	Chemical Structure
BYF 14182-pentanoic acid, isomer 1 and 2	4-(2-{[(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl)-2-methylpentanoic acid	
BYF 14182-desmethyl-pentanoic acid	4-(2-{[(5-fluoro-3-methyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl)-2-methylpentanoic acid	
BYF 14182-3,4,4'-trihydroxy	N-[2-(3,4-dihydroxy-1,3-dimethylbutyl)-4-hydroxyphenyl]-5-fluoro-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-desmethyl-dihydroxy-ketone	5-fluoro-N-{2-[3-hydroxy-1-(hydroxymethyl)-3-methyl-2-oxobutyl]phenyl}-3-methyl-1H-pyrazole-4-carboxamide	
BYF 14182-desmethyl-hydroxymethyl-pentanoic acid*	4-[2-({[5-fluoro-3-(hydroxymethyl)-1H-pyrazol-4-yl]carbonyl}amino)phenyl]-2-methylpentanoic acid	
BYF 14182-desmethyl-3-hydroxy-keto-carboxylic acid*	5-fluoro-4-{[2-(3-hydroxy-1,3-dimethyl-2-oxobutylyl]phenyl]carbamoyl}-1H-pyrazole]-3-carboxylic acid	
BYF 14182-2,3,4-trihydroxy	1,2-dideoxy-2-(2-{[(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl)-4-C-methylpentitol	

Table A2. Chemical structure, codes and chemical names of penflufen metabolites.

Common Names / Code	IUPAC Name	Chemical Structure
BYF 14182-desmethyl-4-carboxylic acid	5-fluoro-3-methyl-1H-pyrazole-4-carboxylic acid	
BYF 14182-pyrazolyl-AAP AE 2300037	*N*-(2-acetylphenyl)-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide	

Attachment 2. Field Trial Geographic Distribution

Table A3.1 Location and Number of North American Potato Field Trials

Type of Formulation[1]	Crop	NAFTA Region	No. of Trials Submitted	No. of Trials Requested	
				Canada	US
240FS	Potato	1	7	5	2
		2	1		1
		3	1		1
		5	5	1	4
		7A	1	1	
		8			
		9[2]	1		1
		10	1		1
		11	6		6
		12	1	1	
		14	2	2	
		Total	26	10	16

[1] 240FS is a flowable concentrate containing 240 g/L of BYF 14182
[2] This trial was actually conducted in Region 8, 14 miles east of the border with Region 9.

Table A3.2 Location and Number of Legume Trials

NAFTA Growing Region [a]	Succulent Bean		Succulent Pea		Dry Bean		Dry Pea	
	Submitted	Requested	Submitted	Requested	Submitted	Requested	Submitted	Requested
1	1	1	2	2				
5	2	2	3	3	2	2	1: vines, hay 1: vines, hay, seed[c]	2
7A					1	1		
11					1: hay & seed 1: forage, hay, seed [b]	1 [d]	1	1
14							4	
Total	3	3	5	5	4 forage 5 hay, seed [b,e]	4	7 vines, hay 6 seed [c,e]	7

[a] The total number of required NAFTA field trials was reduced based on findings in the metabolism and TRR studies during discussions with US EPA (Chem SAC minutes 12/12/2007) and PMRA (PMRA, memorandum Feb. 21, 2008).
[b] Dry bean trial EL059-08HA did not collect forage, so an additional Region 11 trial was initiated which collected dry bean forage, hay, and seed. Data for dry bean forage was collected from four trials, and data for dry bean hay and seed were collected from five trials.
[c] The seed samples from dry pea trial EL061-08HA were lost during storage at BRP. Data for dry pea vines and hay were collected seven trials, and data for dry pea seed were collected from six trials.
[d] One trial from either Region 10 or Region 11 is requested.
[e] Overall, pea and bean seed samples were collected from 19 trials compared with 19 requested trials. Pea and bean forage (vines) samples were collected from 11 trials compared with 11 requested trials. Pea and bean hay samples were collected from 12 trials compared with 11 requested trials.

Table A3.3 Location and Number of North American Potato Field Trials

Type of Formulation[1]	Crop	NAFTA Region	No. of Trials Submitted	No. of Trials Requested	
				Canada	US
240FS	Soybean	2	1		1
		4	1		1
		5	5	2	3
		Total	7	2	5

[1] 240FS is a flowable concentrate containing 240 g/L of BYF 14182
[2] The total number of required NAFTA field trials was reduced based on findings in the metabolism and TRR studies during discussions with US EPA (Chem SAC minutes 12/12/2007) and PMRA (PMRA, memorandum Feb. 21, 2008).

Table A3.4 Location and Number of North American Wheat Field Trials

Type of Formulation[1]	Crop	NAFTA Region	No. of Trials Submitted	No. of Trials Requested[2]	
				Canada	US
240FS	Wheat	5	2	1	1
		7	3	2	1
		8	2		2
		14	2	2	
		Total	9	5	4

[1] 240FS is a flowable concentrate containing 240 g/L of BYF 14182
[2] The total number of required NAFTA field trials was reduced based on findings in the metabolism and TRR studies during discussions with US EPA (Chem SAC minutes 12/12/2007) and PMRA (PMRA, memorandum Feb. 21, 2008).

Table A3.5 Location and Number of North American Barley Field Trials

Type of Formulation[1]	Crop	NAFTA Region	No. of Trials Submitted	No. of Trials Requested[2]	
				Canada	US
240FS	Barley	5	2	2	-
		7	2	2	-
		14	8	8	-
		Total	12	12	-

[1] 240FS is a flowable concentrate containing 240 g/L of BYF 14182
[2] The total number of required NAFTA field trials was reduced based on findings in the metabolism and TRR studies during discussions with US EPA (Chem SAC minutes 12/12/2007) and PMRA (PMRA, memorandum Feb. 21, 2008). Note the US did not require trials in barley.

Table A3.6 Location and Number of North American Corn Field Trials

Type of Formulation[1]	Crop	NAFTA Region	No. of Trials Submitted	No. of Trials Requested[2]	
				Canada	US
240FS	Corn	1	1		1
		5	7	1	6
		11	1		1
		Total	9	1	8

[1] 240FS is a flowable concentrate containing 240 g/L of BYF 14182
[2] The total number of required NAFTA field trials was reduced based on findings in the metabolism and TRR studies during discussions with US EPA (Chem SAC minutes 12/12/2007) and PMRA (PMRA, memorandum Feb. 21, 2008).

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Chemical Name: **Penflufen**

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HED File Code: **11000 Chemistry Reviews**
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11/23/2011