Proposed Registration Decision PRD2012-02

Penflufen

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Overview

Proposed Registration Decision for Penflufen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of the technical product PENFLUFEN TC and its associated end-use products PEN 240FS, PENRED 240FS, PENPRO 118FS, PENPROME 177FS and PENTRI 308FS, containing the fungicidal active ingredient penflufen, for control of various seed-, seedling- and soil-borne diseases on oilseed and cereal grain crops, legume vegetables, alfalfa and potatoes.

A number of these penflufen products are also formulated with the active ingredients clothianidin, metalaxyl, prothioconazole and/or trifloxystrobin. These co-active ingredients are already registered for use as seed treatments in Canada. For a summary of the evaluation of use expansions of prothioconazole and trifloxystrobin to additional crops, please consult the Evaluation Reports in the PMRA's public e-Registry under Application Numbers 2010-1275 and 2010-1284, respectively.

It should be noted that, although full registration is proposed for the end-use product PENPROME 177FS, the PMRA is proposing conditional registration for the use of PENPROME 177FS on small grains due to the registration status of this use for the precedent prothioconazole seed-treatment product, JAU 6476 100 FS Seed Treatment Fungicide (Registration Number 30101).

The PMRA, under the authority of the *Pest Control Products Act* and Regulations, will be granting conditional registration for the sale and use of the end-use products PENCLO 273.5FS and PENCLOTRIME 310.68FS due to the registration status of the precedent clothianidin seed-treatment products, Titan ST Insecticide (Registration Number 27449) and Prosper FX Flowable Insecticide and Fungicide Seed Treatment (Registration Number 29159).

An evaluation of available scientific information found that, under the approved conditions of use, the proposed penflufen products have value and do not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of PENFLUFEN TC, PEN 240FS, PENRED 240FS, PENPRO 118FS, PENCLO 273.5FS, PENCLOTRIME 310.68FS, PENPROME 177FS and PENTRI 308FS.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g., children) as well as organisms in the environment (e.g., those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides & Pest Management portion of the Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on penflufen, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on penflufen, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Penflufen?

Penflufen is a systemic, xylem-mobile fungicide. This active ingredient belongs to the Group 7 of the Fungicide Resistance Action Committee. Penflufen is classified as a succinate dehydrogenase inhibitor (SDHI) and interferes with fungal respiration. Seven penflufen-containing products are proposed for registration.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

4 Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Health Considerations

Can Approved Uses Of Penflufen Affect Human Health?

Penflufen is unlikely to affect your health when used according to label directions.

Potential exposure to penflufen may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient penflufen was of low acute toxicity by the oral, dermal and inhalation routes. Penflufen was minimally irritating to the eye and non-irritating to the skin, and did not cause an allergic skin reaction.

The acute toxicity of the seven end-use products PEN 240FS, PENRED 240FS, PENPRO 118FS, PENCLO 273.5FS, PENCLOTRIME 310.68FS, PENPROME 177FS and PENTRI 308FS containing penflufen was low via the oral, dermal and inhalation routes of exposure. All the end-use products were non to minimally irritating to the eye and non-irritating to the skin, and did not cause allergic skin reactions.

There was no indication that the technical grade active ingredient penflufen caused damage to the nervous system. There was a low level of concern for effects on the immune system. Health effects in animals given repeated doses of penflufen over a long period of time were decreases in body weight, and changes to the liver, thyroid, blood, adrenals and kidneys.

There was no evidence to suggest that penflufen damaged genetic material. Penflufen did, however, cause brain, ovarian and blood-related tumours in rats. The cancer risk assessment was conducted based on the ovarian tumours found in rats as this was protective of the other tumour types.

Penflufen did not cause birth defects in animals. A decreased number of pups per dam at birth was observed at a dose that was toxic to the maternal animals. When penflufen was given to pregnant or nursing animals, effects indicating a delay in development in the fetus and juvenile animal (e.g., decreased fetal weight, incomplete ossification and delay in sexual maturation) were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to penflufen than the adult animal.

The risk assessment protects against the effects of penflufen by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues In Water And Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants less than one year old, the subpopulation which would ingest the most penflufen relative to body weight, are expected to be exposed to less than 6% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from penflufen is not of concern for all population subgroups. The lifetime cancer risk from the use of penflufen on cereal grains, oilseeds, legume vegetables, potato and alfalfa is considered acceptable.

Acute dietary (food and water) estimates for the general population and all population subgroups were less than 6% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was infants less than one year old.

The Food and Drugs Act (FDA) prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the Pest Control Products Act (PCPA). Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using penflufen on potatoes, beans, peas, soybeans, wheat, barley, sweet corn, field corn, sunflower, canola and cotton were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document.

Risks In Residential And Other Non-Occupational Environments

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity, such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

Occupational Risks From Handling Penflufen Products

Occupational risks are not of concern when penflufen products are used according to the proposed label directions, which include protective measures.

Workers treating seed with penflufen products in commercial seed treatment facilities, workers treating seed on-farm and workers planting treated seed can come into direct contact with penflufen residues on the skin. Therefore, anyone treating seed with seed treatment products containing penflufen or bagging treated seed, handling bags of treated seed or cleaning

equipment used to treat seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves. Closed transfer is required for seeds treated at commercial seed treatment facilities. For products co-formulated with other active ingredients, the personal protective measures required reflect those required for other seed treatment products containing the same active ingredients. Taking into consideration these precautionary measures, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

Environmental Considerations

What Happens When Penflufen Is Introduced Into The Environment?

Penflufen enters the environment when used as an in-furrow treatment on potato seed pieces and as a seed treatment for various crops. Once in the terrestrial environment, penflufen moderately binds to soil particles and has moderate to low potential for leaching. Penflufen is moderately persistent to persistent in soil. In aquatic systems, penflufen will move from the water column into the sediment where it will persist. Residues of penflufen are not expected to be found in air due to low volatility.

Penflufen is toxic to aquatic organisms; however, based on the use of penflufen as a seed treatment and in-furrow application, the potential for exposure to non-target organisms is expected to be limited. Risks to both non-target terrestrial and aquatic organisms from the use of penflufen were determined to be acceptable.

Value Considerations

What Is The Value Of Penflufen Products?

Penflufen products are formulated as seed treatments for control of seed, seedling and soil-borne diseases on various oilseed and cereal grain crops, legume vegetables, alfalfa and potatoes. Penflufen represents an effective disease management tool and would also be the first fungicide registered for certain diseases on crops such as winter wheat, sunflower, safflower, flax, crambe and borage. A number of the penflufen fungicides contain a combination of actives in order to achieve effective resistance management and/or to increase the spectrum of controlled pests.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the product labels to address the potential risks related to the hazards of penflufen are as follows.

Key Risk-Reduction Measures

Human Health

Anyone treating seed with penflufen or bagging treated seed, handling bags of treated seed or cleaning equipment used to treat seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves.

Closed transfer is required for seeds treated at commercial seed treatment facilities.

Environment

Standard precautionary measures are required to minimize potential exposure of aquatic habitat.

Treated seeds must be incorporated into the soil as a standard precautionary measure to minimize potential exposure of birds and mammals that might feed on exposed seed.

Next Steps

Before making a final registration decision on penflufen, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency’s response to these comments.

Other Information

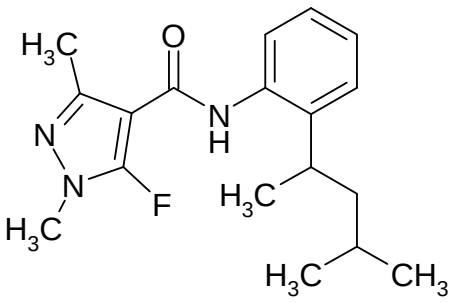
When the PMRA makes its registration decision, it will publish a Registration Decision on penflufen (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA’s Reading Room (located in Ottawa).

Science Evaluation

Penflufen

1.0 The Active Ingredient, Its Properties And Uses

1.1 Identity Of The Active Ingredient

Active substance	Penflufen
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2'-[(*RS*)-1,3-dimethylbutyl]-5-fluoro-1,3-dimethylpyrazole-4-carboxanilide
2. Chemical Abstracts Service (CAS)	1*H*-pyrazole-4-carboxamide, N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-
CAS number	494793-67-8
Molecular formula	$C_{18}H_{24}FN_3O$
Molecular weight	317.41 g/mol
Structural formula	
Purity of the active ingredient	98.72%

1.2 Physical And Chemical Properties Of The Active Ingredient And End-Use Products

Technical Product — PENFLUFEN TC

Property	Result
Colour and physical state	Pure: off-white powder Technical: powder varying in colour from colourless to white or pale green/blue/pink
Odour	Weak, not characteristic
Melting range	Pure: 111.1 °C Technical: 107.6 °C
Boiling point or range	n/a
Relative density	1.21
Vapour pressure at 20°C	4.1×10^{-7} Pa (extrapolated)
Henry's law constant at 20°C	1.05×10^{-5} Pa · m^3 · mol^{-1}
Ultraviolet (UV)-visible spectrum	Peak maxima at ~205 and ~230 nm; no absorption at $\lambda > 300$ nm
Solubility in water at 20°C	At pH 6.5, 12.4 mg/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) methanol 126 n-heptane 1.6 toluene 62 dichloromethane > 250 acetone 139 ethylacetate 96 dimethyl sulfoxide 162
n-Octanol-water partition coefficient (K_{ow})	At pH 7, log K_{ow} = 3.3
Dissociation constant (pK_a)	No dissociation observed between pH 1 and 12
Stability (temperature, metal)	Stable in the presence of metals and metal ions at elevated temperature (54˚C) for two weeks.

End-Use Products — PEN240FS, PENRED 240FS, PENPRO118FS, PENCLO 273.5FS

Property	PEN 240FS	PENRED 240FS	PENPRO 118FS	PENCLO 273.5FS
Colour	White	Red	Red	Beige
Odour	Slight chemical odour		Paint-like	Faint sweet
Physical state	Liquid			
Formulation type	Suspension (flowable concentrate)			
Guarantee	Penflufen 240 g/L		Penflufen 100 g/L Prothioconazole 18 g/L	Penflufen 66.7 g/L Clothianidin 207 g/L
Container material and description	HDPE bottle / canister, 0.25 – 10 L, or canister / IBC such as 1000 L			
Density	1.057 g/mL	1.078 g/mL	1.066 g/mL	1.11 g/mL
pH of 1% dispersion in water	5.9	6.3	5.6	5.15 undiluted
Oxidizing or reducing action	None			
Storage stability	Stable over 12 months in HDPE packaging			Stable over 13 months in HDPE packaging
Corrosion characteristics	Not corrosive in HDPE packaging			
Explodability	Not explosive			

End-Use Products — PENCLOTRIME 310.68FS, PENPROME 177FS, PENTRI 308FS

Property	PENCLOTRIME 310.68FS	PENPROME 177FS	PENTRI 308FS
Colour	Light blue	Beige	Dark blue-violet
Odour	Musty		
Physical state	Liquid		
Formulation type	Suspension (flowable concentrate)		
Guarantee	Penflufen 10.7 g/L Clothianidin 290 g/L Trifloxystrobin 7.15 g/L Metalaxyl 7.15 g/L	Penflufen 38.4 g/L Prothioconazole 76.8 g/L Metalaxyl 61.4 g/L	Penflufen 154 g/L Trifloxystrobin 154 g/L
Container material and description	HDPE bottle / canister, 0.25 – 10 L, or canister / IBC such as 1000 L		

Property	PENCLOTRIME 310.68FS	PENPROME 177FS	PENTRI 308FS
Density	1.308 g/mL	1.075 g/mL	1.169 g/mL
pH of 1% dispersion in water	8.6	6.5	9.2
Oxidizing or reducing action	None		
Storage stability	Study is ongoing		Stable over 12 months in HDPE packaging
Corrosion characteristics	Study is ongoing		Not corrosive to its HDPE packaging
Explodability	Not explosive		

1.3 Directions for Use

Penflufen products are intended for control of various seed-, seedling- and soil-borne diseases on oilseed and cereal grain crops, legume vegetables, alfalfa and/or potatoes. They are to be used in commercial seed treatment operations and for on-farm treatment with conventional seed treating equipment. PEN 240FS may also be used as an in-furrow application for control of soil-borne black scurf on potatoes. Certain tank-mixes with fungicide and insecticide seed treatments are proposed on specific crops.

1.4 Mode of Action

Penflufen is an alkylamide fungicide belonging to the chemical classes of carboxamides (SDHI or Group 7 Fungicide). This active ingredient is xylem-mobile and acts by interfering with the normal respiration process in susceptible fungi.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in PENFLUFEN TC have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The methods provided for the analysis of the active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for Residue Analysis

High performance liquid chromatography with mass spectrometry (HPLC-MS/MS) methods were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective limits of quantitation of the methods. Acceptable recoveries (70-120%) were obtained in plant, animal, soil, sediment and water matrices. The proposed enforcement methods were successfully validated in several plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples of several crop matrices and animal tissues analyzed with the respective enforcement methods. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Penflufen is a fungicide belonging to the carboxamides group. A detailed review of the toxicological database for penflufen was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to penflufen.

Following a single oral radiolabelled dose in rats, penflufen was rapidly and almost completely absorbed from the gastrointestinal tract (GIT). Regardless of the exposure regimen, the maximum concentration of penflufen in blood and plasma was reached within 1 hour of dosing and declined rapidly by 72 hours in both sexes. The elimination half-life of penflufen was similar in both sexes and was approximately 20-24 hours. The area under the curve ($AUC_{0-\infty}$) value for females was ~1.5-fold higher than males, suggesting a higher systemic exposure for female rats. The majority of excretion occurred within the first 24 hours and was nearly complete after 72 hours in both sexes. The predominant route of elimination in male rats was fecal via the bile. In low dose females, approximately equal amounts of radioactivity were detected in both the feces and urine. Less than 0.1% of the administered dose (AD) was measured in expired air of both sexes. The distribution pattern of radioactivity was similar between sexes. The maximum total radioactive residue (TRR) was reached for all organs and tissues at 1 hour post dosing and a similar distribution was observed throughout the experiment period. The highest TRRs were detected in the liver, erythrocytes and the kidneys. Under the conditions of the studies, there was no evidence of bioaccumulation in either sex.

Penflufen was extensively metabolized. There were no significant differences in metabolic pathways between dose groups and sexes, however sex-specific quantitative differences in the pattern of metabolites were observed. The parent compound was detected at a low amount only in feces, representing less than 2.0% of the AD. The majority of metabolites (58-94% of the AD) were identified. The main pathways of metabolism involved demethylation of the pyrazole ring or hydroxylation of the side chain of the phenyl ring, position 4’ of the phenyl ring and the

methyl group in position 3 of the pyrazole ring. The hydroxylation of position 3 of the alkyl side chain led to the intermediate BYF 14182-3-hydroxy-butyl. This metabolite was detected only in the bile at a very low amount, but was shown to be a key systemic intermediate in the metabolism of penflufen. The toxicokinetic and metabolic behaviours of penflufen and BYF 14182-3-hydroxy-butyl were similar. Further oxidation of the hydroxyl groups led to keto or carboxylic acid compounds. Cleavage of the alkyl side chain and further oxidation, and cleavage of the carboxamide bond or N-phenyl bond resulted in other minor metabolites. Results of the toxicokinetics and metabolism studies with penflufen are summarized in Appendix I, Table 2.

BYF 14182-3-hydroxy-butyl and BYF 14182-pyrazolyl-AAP were identified as major soil metabolites. Of these two metabolites, only the hydroxyl-butyl form was also identified in the rat. The genotoxic potential of these two metabolites was tested with the reverse mutation assay, gene mutation assay in mammalian cells and chromosomal aberration assay, and all results were negative (Appendix I, Table 3).

Penflufen was of low acute toxicity by the oral, dermal and inhalation routes in rats. It is minimally irritating to the eye and non-irritating to the skin of rabbits. Penflufen is not a dermal sensitizer in guinea pigs (maximization test of Magnusson and Kligman).

The penflufen end-use products were of low acute toxicity via the oral, dermal and inhalation routes in rats. They were non to minimally irritating to the eye and non-irritating to the skin of rabbits. None of these end-use products were dermal sensitizers in mice (local lymph node assay).

In subchronic and chronic toxicity studies, penflufen produced systemic toxicity manifested as decreased body weight and specific target organ toxicity in the liver and thyroid of all test species (rat, mouse and dog), in the kidneys and hematopoietic system of two species (rat and mouse) and in the adrenals of one species (dog).

From short-term to long-term studies, there was a progression from adaptive liver changes to hepatotoxicity in rats, while no clear progression in severity of the liver was observed in mice or dogs. Liver toxicity included increased weight, liver enlargement, darkening and/or brown pigmentation, clinical chemistry alterations (including changes in cholesterol levels, bilirubin levels, total protein levels, albumin levels and several liver enzyme activity levels) and associated histopathological findings (e.g., liver hypertrophy). In short-term studies (90-day), prominent lobulation of the liver was also observed in rats, and multifocal intra-hepatocellular eosinophilic material and multifocal perilobular single cell death were noted in dogs. Following 24 months of dosing, rats also exhibited focal oval cell hyperplasia, hepatocellular single cell necrosis and diffuse or focal degeneration/necrosis and hepatocellular macrovacuolation (also observed in mice at 18-month post-dosing). Thyroid toxicity consisted of increased weight, thyroid enlargement or darkening, follicular cell brown pigment, diffuse follicular cell hypertrophy, colloid alteration and follicular hyperplasia. The majority of the thyroid histopathological findings occurred following long-term exposure (18 months in mice, 24 months in rats, 12 months in dogs). Toxicity of the hematopoietic system included decreased leucocyte counts and increased incidence of single cell death in the thymus of mice, increased

prothrombin time and platelet counts in dogs, and decreased thymus weight associated with increased incidence of small thymus in rats. Pathology of the adrenals in dogs involved increased weight, diffuse cortical hypertrophy/hyperplasia and focal/multifocal zona glomerulosa vacuolation. In rats and mice, kidney toxicity was evidenced by decreased weight, unilateral fibrosis/atrophy of the kidneys and hyaline droplet nephropathy. In addition to the organ specific effects observed above, decreased body weight, body weight gain and food consumption were noted throughout the database. In general, longer term dietary dosing demonstrated the same target organs as seen in shorter term dosing. All the adverse effects noted in treated rats following 12 months of treatment were resolved in a recovery group following a period of 13 weeks, with the exception of bilirubin levels in males, which only partially recovered.

A 28-day dermal toxicity study in rats did not result in any dermal or systemic toxicity. The dosing was considered adequate based on the use of a limit dose.

There was no evidence of carcinogenic potential in mice, however an increased incidence of ovarian tubulostromal adenomas associated with an increased incidence of focal tubulostromal hyperplasia of the ovaries were noted in high-dose females in the 24-month rat combined chronic/carcinogenicity study. Increased incidences of malignant brain astrocytomas and histiocytic sarcomas in high-dose males were also observed. As no mode of action framework for the above tumours was provided, a linear low-dose extrapolation approach was used for the cancer risk assessment.

No evidence of mutagenic potential of penflufen was observed in a battery of *in vitro* and *in vivo* genotoxicity assays including reverse Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.mutation assay, gene mutation assay in mammalian cells, chromosomal aberration assay and micronucleus assay.

In the 2-generation reproductive toxicity study, the parental animals showed decreased body weight and body weight gain, alteration in food consumption, decreased thymus weight and increased thyroid weight at the highest dose tested (HDT). The offspring showed decreased body weight and body weight gain during lactation, decreased spleen weight and increased relative brain weight at the HDT. Delay in vaginal opening and preputial separation was also observed in both generations at the HDT, but occurred in the presence of maternal toxicity. Reproductive toxicity was evidenced by decreased litter size at birth in the high dose.

There was no evidence of increased susceptibility of the young in the oral rat and rabbit developmental toxicity studies compared to the maternal animals. Maternal rats and rabbits exhibited decreased body weight gain and food consumption at the HDT. The litters in the rabbit developmental study showed decreased fetal weight and incomplete ossification of the 5^{th} and 6^{th} sternebrae at the HDT, while rat fetuses revealed no adverse effects.

Penflufen was not neurotoxic as demonstrated in the acute and 90-day neurotoxicity studies in rats. Decreased motor and locomotor activity levels were observed, but at systemically toxic doses. Based on the toxicology database of penflufen, there was a low level of concern for effects on the immune system.

Results of the toxicology studies conducted on laboratory animals with penflufen and its associated end-use products are summarized in Appendix I, Tables 4 and 5, respectively. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 6.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a time frame. Information on the reporting of incidents can be found on the Pesticides & Pest Management portion of the Health Canada's website. Incidents from Canada and the United States were searched and reviewed for the active ingredient penflufen. As of August 9th 2011, the PMRA had received no incident reports for products containing penflufen.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for penflufen. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. Minor developmental effects including decreased fetal weight and increased incidence of incomplete ossification of the 5th and 6th sternebrae (skeletal variation) were observed in the rabbit developmental toxicity study; however, these effects occurred in the presence of maternal toxicity. In the 2-generation rat reproductive toxicity study, serious effects in the form of decreased litter size, as well as a delay in vaginal opening and preputial separation in the offspring, were observed at the HDT; however, these occurred in the presence of maternal toxicity (body weight and food consumption effects). Overall, endpoints in the young were well-characterized and the endpoints selected for risk assessment are protective of the effects observed. On the basis of this information, the PCPA factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose (ARfD)

General population (including females 13-49 years of age)

To estimate acute dietary risk (1 day), the acute neurotoxicity study with a NOAEL of 50 mg/kg bw was selected for risk assessment. At the LOAEL of 100 mg/kg bw, decreased motor and locomotor activity levels were observed in females. These effects occurred on the first day of dosing and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold.

The composite assessment factor (CAF) is 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD (gen. pop)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{50 \text{ mg/kg bw}}{100} = 0.5 \text{ mg/kg bw of penflufen}$$

The selection of this endpoint and CAF is considered protective of all populations, including pregnant women and their fetuses.

3.3 Determination of Acceptable Daily Intake (ADI)

To estimate dietary risk of repeat exposure, the 24-month combined chronic/carcinogenicity study with a NOAEL of 4 mg/kg bw/day was selected for risk assessment. At the LOAEL of 79 mg/kg bw/day, decreased body weight, body weight gain (females), food consumption (females), alkaline transaminase (ALT) activity levels, bilirubin levels, and increased cholesterol levels (females) and liver weight associated with gross and histopathological findings were observed. This study provides the lowest NOAEL in the toxicology database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. **The CAF is 100.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{4 \text{ mg/kg bw/day}}{100} = 0.04 \text{ mg/kg bw/day of penflufen}$$

The ADI provides margins of 1898 and 2500 to the NOAEL for the 2-generation toxicity in the rat study and developmental toxicity in the rabbit, respectively, and consequently, is considered to be protective of pregnant women and their fetuses.

Cancer assessment

In the 24-month combined chronic/carcinogenicity rat study, ovarian tubulostromal adenomas in high-dose females, and malignant brain astrocytomas and histiocytic sarcomas in high-dose males were observed. In the absence of a submitted mode of action framework for the above tumours, a linear low-dose extrapolation approach (q_1*) was used for penflufen. An adjusted q_1* value of 2.59×10^{-3} $(mg/kg\ bw/day)^{-1}$ was derived for the ovarian tubulostromal adenomas and was selected for the cancer risk assessment as it was the highest value of the three tumours.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to seed treatment products containing penflufen is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation routes.

Short-term and intermediate-term dermal

For short- and intermediate-term dermal risk assessment, the 28-day dermal rat study was selected. It was determined that the highest dermal absorption value from the *in vivo* rat study was approximately 6.3% (see section 3.4.1.1), therefore the limit dose of 1000 mg/kg bw/day from the 28-day dermal rat study was sufficiently protective of the endpoints regarding the offspring and developmental toxicity observed in the 2-generation reproductive study (the NOAEL of 75.9 mg/kg bw/day for the 2-generation study (expressed as dermal equivalent of 75.9 ÷ 0.06 = 1265 mg/kg bw/day) exceeded the systemic limit dose of 1000 mg/kg bw/day). Consequently, a NOAEL of 1000 mg/kg bw/day from the 28-day dermal rat study was selected.

The target Margin of Exposure (MOE) for this endpoint is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short-term and intermediate-term inhalation

For short-term and intermediate-term inhalation risk assessment, the 90-day dog study was considered to be the most appropriate. Therefore, a NOAEL of 55.7 mg/kg bw/day from the 90-day dog study was selected for the risk assessment. At the LOAEL of 532 mg/kg bw/day, decreased body weight and body weight gain (females), food consumption, cholesterol, albumin, albumin/globulin ratio and total protein (males) levels, and increased platelet counts (females), prothrombin time, γ-glutamyl-transferase and alkaline phosphatase activity levels, thyroid weight (males), liver weight associated with histopathological findings, and adrenal weights with associated histopathology (males) were observed.

The target MOE for this endpoint is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this endpoint and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Cancer assessment

Please refer to Section 3.3.

3.4.1.1 Dermal Absorption

In support of the penflufen applications, an *in vivo* dermal absorption study in rats and an *in vitro* dermal absorption study in rat and human skin were submitted. The submitted dermal penetration studies for penflufen were of good quality and the 'triple pack' approach was considered for setting a dermal absorption value. However, the percent of dermally absorbed dose in the rat *in vitro* studies is three fold higher than in the rat *in vivo* studies, with a ratio of 3.2. As such, it was considered appropriate to use the *in vivo* dermal absorption value to determine a dermal absorption value for use in the risk assessment for penflufen. The highest mean dermal absorption value measured in the two lowest doses was approximately 6.3 % including skin bound residues. At the lowest dose, the highest dermal absorption value was measured eight hours after application; at the mid-level dose, the highest mean dermal absorption value was measured 72 hours after application.

As a result, the dermal absorption value of **6.3%** was selected for use in the cancer risk assessment for penflufen. This value may need to be reconsidered for formulations and uses other than those currently proposed for registration.

3.4.2 Occupational Exposure and Risk

Based on similarities in morphology, agronomic practices and/or dust off potential, proposed seeds were clustered into five groups:

1) oilseeds and alfalfa – including canola, rapeseed, mustard, flax, linseed, crambe, borage, sunflower and safflower
2) legumes – including dry beans and peas
3) cereals – including wheat, barley, oats, buckwheat, millet, rye, and triticale
4) corn and sorghum
5) potato seed pieces

For all seed groups, both commercial and on-farm seed treatment is proposed. For potato seed pieces, commercial and on-farm seed treatment are proposed along with in-furrow application.

3.4.2.1 Commercial seed treatment exposure

Individuals have potential for exposure to seed treatment products containing penflufen and its coformulants while treating seed in commercial seed treatment facilities. Chemical specific data for assessing human exposure during commercial seed treatment were not submitted. As such, generic exposure data have been used to estimate risk to workers in commercial seed treatment facilities.

3.4.2.1.1 Cereal Seeds

One study measured exposure to four workers treating wheat with imidacloprid at commercial seed treatment facilities. In all trials, wheat seed was treated with GAUCHO 480 SC, containing imidacloprid at a target rate of 3.94 g a.i./45 kg seed. The average replicate length for all sites was 8.5 hours. Treated wheat seed was not bagged. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn under a single layer of clean clothing. Workers wore normal work clothing and gloves and most wore a hat and glasses. Inhalation exposure for each worker was measured by means of a personal air sampling pump with an OVS tube containing a fibre filter and XAD-2 adsorbent.

Since this exposure study was conducted on wheat and bagging of cereal grain seed is rarely done, it is considered to be appropriate for estimating exposure to workers treating cereal seeds at commercial seed treatment facilities. Only four commercial replicates were measured in this study, and the amount of seed handled and the amount of active ingredient handled in the study are significantly lower than the expected use pattern for penflufen. As such, it was considered appropriate to use the 90^{th} percentile unit exposure values from the study to estimate exposure to commercial treatment workers.

A submitted dust off study demonstrated similar dust off potential for wheat and barley, with the dust off values for oats being approximately ten fold higher. Given the results of the submitted dust off study, the surrogate study on wheat is not expected to underestimate exposure for barley, but it may underestimate the exposure for oats. No dust off data were submitted for rye or triticale.

The non-cancer and cancer exposure and risk estimates are summarized in Appendix I, Tables 7 and 8, respectively for penflufen when workers treat cereal seed with seed treatment products containing penflufen. Calculated MOEs are above the target MOEs for all workers in commercial seed treatment facilities. Cancer risk for commercial workers treating cereal grains was estimated by calculating a lifetime average daily dose (LADD). An exposure duration of 60 days was assumed for commercial treaters. Although this may be a high end estimate, this value was considered appropriate as cereal seeds may be treated for several months. Cancer risk for these workers is not expected to exceed 1.0×10^{-5} and therefore is not of concern.

Given that the calculated MOEs are well above the target MOEs and cancer risk is 1.0×10^{-6}, and the fact that less oat seed is expected to be treated than wheat seed, exposure to workers treating oat seeds in commercial facilities are not expected to be of concern even though the dust off potential for oats was higher than that for wheat. Given the high MOEs, and low cancer risk, it was determined that further confirmatory dust off data for rye and triticale were not required.

3.4.2.1.2 Oilseed, alfalfa, legume, corn and sorghum seed

The applicant submitted a study designed to determine the dermal and inhalation exposure of experienced agricultural workers performing commercial canola or corn seed treatment activities using continuous flow or continuous batch systems. The seeds were treated with flowable seed treatment products containing one or more of the active ingredients clothianidin, carbathiin, and metalaxyl at label rates. The treatment involved closed transfer of the active ingredients. The study was conducted at two canola seed treatment facilities in Canada, and three corn seed treatment facilities in the United States.

A total of 24 male workers were monitored during the study. Dermal exposure was estimated by measuring residues on or in inner whole body dosimeters, face/neck wipes, and hand washes. Inhalation exposure was estimated by measuring residues in personal air samplers fitted with an OVS tube. Three different job activities were monitored at the sites: 1) treatment of seed, including mixing, loading and operation of the seed treatment equipment; 2) packaging of treated seeds, including bagging, sewing, stacking and forklift operations; and 3) cleaning of seed treatment and seed handling equipment. The treatment solutions were prepared using closed transfer systems into the seed treatment equipment.

Dermal exposure was clustered into four groups in the interest of simplicity and utility of the data groups (single layer and gloves, single layer and no gloves, coveralls and gloves and coveralls and no gloves). The single layer groups include data for workers wearing long sleeved shirts and long pants, long or short-sleeved shirts, pants and a jacket or sweatshirt, and long sleeved shirts, long pants and chemical resistant aprons. The coveralls groups include data for workers wearing long or short-sleeved shirts, pants and coveralls. The gloved groups include workers wearing chemical resistant or work gloves, and the non-gloved groups include only workers not wearing any gloves. Given this clustering scheme, the dermal data for the single layer group may underestimate exposure for workers wearing single layer since the data are based on workers wearing more personal protective equipment (i.e. jacket or sweatshirt or chemical resistant apron). Exposure for workers wearing gloves may overestimate exposure for workers wearing chemical resistant gloves since some workers wore work gloves which may not be as protective as chemical resistant gloves. Exposure from all sites and seed types was combined since the equipment used, exposure duration and exposure potential are expected to be similar.

The dermal and inhalation exposure values are expressed as µg/kg a.i. handled for treaters and bagger/sewer/stackers. The dermal exposure of equipment cleanout operators is provided in µg/g a.i./100 kg seed (i.e. normalized by application rate). As it is not possible to determine the amount of active ingredient handled per day for cleaners, exposure to these workers was normalized by the mean application rate used over the treatment period. For cleaners, the single layer and gloves data are based on cleaners in facilities treating corn, and for coveralls and gloves, the data are based on workers cleaning facilities treating canola. It should be noted that the corn cleaners had a monitoring duration of less than two hours, whereas the canola cleaners had an average exposure duration of 8.35 hours. Field recovery for OVS tubes for carbathiin was low for the two lowest doses. Given this low recovery and the small sample size for carbathiin, it was considered appropriate to exclude the inhalation exposure for carbathiin from the calculation of inhalation exposure for seed treatment workers.

To estimate exposure to workers treating oilseed, alfalfa, legume, corn and sorghum seeds with seed treatment products containing penflufen, this study was considered appropriate since workers were monitored while treating canola and corn seeds, and seeds were bagged after treatment. The dust off potential of canola and corn seeds as well as that for alfalfa, sunflower (oil and confectionary), mustard, peas and beans was measured in the submitted dust off study. For alfalfa and sunflower seeds, only the dust off potential for untreated seeds was provided. The dust off potential for mustard, sunflower and alfalfa seeds was higher than that for corn and canola. As such, the clothianidin/carbathiin/metalaxyl study may underestimate exposure for mustard, sunflower and alfalfa seeds.

For treater/applicators, the highest mean unit exposures for the active ingredients (those for metalaxyl) were considered appropriate for use in the risk assessment since there was a significant difference between the mean values for the different active ingredients for workers wearing a single layer and gloves. Even though there were only nine replicates, a mean value was chosen for use in the risk assessment, since the sample size was relatively high and the study was of high quality. However, this is considered a conservative, Tier one approach. For bagger/sewer/stackers, there was not a large difference between the unit exposures calculated for the active ingredients for workers wearing a single layer and gloves. As such, it was considered appropriate to use the combined arithmetic mean for all the replicates for dermal and inhalation exposure in the risk assessment for commercial workers.

For cleaners, the single layer and gloves scenario is representative of workers cleaning equipment at facilities treating corn, but it is likely that these workers would conduct other activities during the work day since the cleaning only took two hours. However, from the study report, it does not appear that these workers were monitored for any other tasks. A risk assessment was conducted with both the corn and the canola cleaner exposure values; however, this is not expected to cover off all cleaner scenarios for all proposed oilseed, legume, alfalfa and corn crops. Given the high MOEs calculated for commercial workers, cleaner exposure is not expected to be of concern.

Since the amount of active ingredient handled per day is highest for sunflower and safflower seeds (16.3 kg a.i. handled), these seeds were used as a worst case to estimate exposure to commercial seed treatment workers for treater/applicators and for bagger/sewer/stackers. Since cleaner exposure is normalized by application rate, the highest application rate of 15 g a.i./ 100 kg seed for alfalfa and oilseeds was used to calculate exposure. This is considered a worst case, Tier one estimate.

The non-cancer and cancer exposure and risk estimates are summarized in Appendix I, Tables 7 and 8, respectively, for penflufen when workers treat legume, oilseed, alfalfa and corn seed with seed treatment products containing penflufen. Calculated MOEs are above the target MOEs for all workers in commercial seed treatment facilities. Cancer risk for commercial workers treating cereal grains was estimated by calculating a lifetime average daily dose (LADD). An exposure duration of 60 days was assumed for commercial treaters. Although this may be a high end estimate, this value was considered appropriate as oilseeds may be treated for several months. All calculated risks are below 1.0×10^{-5} and are not of concern. No dust off data were provided for safflower, flax, rapeseed, linseed, crambe, borage or sorghum, but the dust off potential for these crops is expected to be similar to other crops and since the calculated MOEs are considerably higher than the target MOE, no further confirmatory data are required.

3.4.2.1.3 Potato Seed Pieces

Exposure estimates for potato seed piece treaters and cutters/sorters in on-farm and commercial operations when wearing single layer and gloves were based on a generic study that measured the exposure of workers treating potato seed pieces with ADMIRE 240 F containing the active ingredient imidicloprid. The total task based exposure value from this study (normalized for the amount of a.i. handled) was considered appropriate for risk assessment purposes. For treaters, the average total task-based dermal and inhalation exposures were 291 µg/kg a.i. handled and 11.5 µg/kg a.i. handled, respectively. For cutter/sorters, the average total task based inhalation exposure was 18.0 µg/kg a.i. handled.

Treating and cutting/sorting were combined by adding the treater dermal exposure and the cutter/sorter inhalation exposure (the higher of the two inhalation exposure values) together. This approach was done, assuming that the treater also cuts and sorts. However, according to data previously submitted by the applicant, the treater may occasionally help out, providing brief relief to a worker on the cutting/sorting line.

The non-cancer and cancer exposure estimates and risk estimates are summarized in Appendix I, Tables 7 and 8, respectively, for workers treating, cutting and sorting potato seed pieces. Calculated MOEs were above the target MOE of 100. Commercial operations workers were assumed to be working for 30 days per year (mid-March to mid-May). Cancer risk estimates for treaters and cutters/sorters were below 1.0×10^{-5} and are not of concern for worker populations. On-farm workers are expected to treat for less than a week per year, compared to the 30 days of treating and cutting/sorting in commercial operations. Non-cancer and cancer risk for treaters and cutters/sorters in on-farm and commercial operations is not of concern when workers wear a single layer and chemical-resistant gloves.

3.4.2.2 On-farm seed treatment exposure

Individuals have potential for exposure to seed treatment products containing penflufen and its coformulants while treating seed on-farm. Chemical specific data for assessing human exposure during on-farm seed treatment were not submitted. As such, generic exposure data have been used to estimate risk to on-farm treaters.

For on-farm seed treatment and planting, the GAUCHO 480 SC study was considered appropriate to address exposure to all proposed crops except potatoes. The study measured exposure to 12 workers treating and planting wheat seed on-farm. In all trials, wheat seed was treated with GAUCHO 480 SC, containing imidacloprid at a target rate of 3.94 g a.i./45 kg seed. The average replicate length for all sites was 8.5 hours. Treated wheat seed was not bagged. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn under a single layer of clean clothing. Workers wore normal work clothing and gloves and most wore a hat and glasses. Inhalation exposure for each worker was measured by means of a personal air sampling pump with an OVS tube containing a fibre filter and XAD-2 adsorbent.

Total exposure to imidacloprid was normalized for each worker based on the amount of active ingredient handled. Information was not available on whether planting was done in an open or closed cab tractor in the GAUCHO 480 SC study. As such, it is assumed that the workers used closed cab equipment during planting.

The submitted dust off study demonstrated similar dust off potential for wheat and barley, with the dust off values for oats being approximately ten fold higher. Given the results of the submitted dust off study, the surrogate study on wheat is not expected to underestimate exposure for barley, but it may underestimate the exposure for oats. No dust off data were submitted for rye or triticale.

The non-cancer and cancer exposure and risk estimates are summarized in Appendix I, Tables 9 and 10, respectively, for penflufen when on-farm workers treat and plant seed treated with seed treatment products containing penflufen. Calculated MOEs are above the target MOEs for all on-farm workers and planters. Cancer risk for on-farm workers treating and planting cereal grains was estimated by calculating an LADD. An exposure duration of ten days was assumed for these workers. Although this may be a high end estimate, this value was considered appropriate as cereal seeds may be treated for several days and several types of seed may be treated. Cancer risk is well below 1.0×10^{-5} and is not of concern. Even though it was assumed that closed cab tractors were used to generate the planting data in the GAUCHO 480 SC study, given the calculated risks, exposure from open cab tractors are not expected to result in risks of concern. Given the high MOEs and low cancer risk, further confirmatory dust off data for rye, triticale, safflower, flax, rapeseed, linseed, crambe, borage and sorghum were not required.

Commercial potato piece treatment exposure estimates are expected to cover off exposure to workers applying penflufen seed treatment products to potato seed pieces on-farm.

3.4.2.3 Planting Exposure

Individuals have potential for exposure to seed treatment products containing penflufen and its coformulants while planting treated seed. Chemical specific data for assessing human exposure during planting were not submitted. As such, generic exposure data have been used to estimate risk to workers planting treated seed.

For cereal seed, given that commercially treated cereal seed is not expected to be bagged, the estimates of exposure for on-farm treating and planting from the GAUCHO 480 SC study are expected to cover off exposure from planting of commercially treated seed. However, oilseeds, alfalfa, legume and corn seeds are usually bagged at commercial facilities, and as such, the GAUCHO 480 SC study is not representative of exposure to workers loading and planting bagged seed.

To address planting exposure from bagged seed, there are two studies available to which the applicant has access. In one study, worker exposure was measured while planting canola seed treated with isofenphos. In the other, worker exposure was measured while planting corn treated with imidicloprid. Both the canola and corn planting studies monitored exposure from workers planting treated seeds from bags, which is the similar exposure scenario as workers who plant oilseeds, legumes, alfalfa and corn seeds treated with seed treatment products containing penflufen in commercial facilities. The limitation of using these two studies as surrogates to estimate planter exposure is that neither study assesses exposure from planting using an open cab tractor.

The canola study was used to estimate planter exposure from the proposed use on oilseeds, alfalfa, and legumes, as the seed type is more similar to canola than to corn. The corn study was used to estimate exposure to workers planting treated corn. The dust off potential of canola and corn seeds as well as that for alfalfa, sunflower (oil and confectionary), mustard, peas and beans was measured in the submitted dust off study. The dust off potential of corn and canola seed treated with penflufen was higher than that for beans and peas; however, the dust off potential for untreated alfalfa, and sunflower seeds and treated mustard seeds are slightly higher than that for corn and canola. As such, the surrogate studies are not expected to underestimate exposure for legumes, but may underestimate exposure from planting alfalfa, sunflower and mustard seeds.

The non-cancer and cancer exposure and risk estimates are summarized in Appendix I, Tables 11 and 12, respectively for penflufen when workers plant oilseed, alfalfa, legume and corn seed treated with seed treatment products containing penflufen. MOEs are well above the target MOEs. Cancer risk for on-farm workers planting seeds was estimated by calculating an LADD. An exposure duration of ten days was assumed for these workers. Although this may be a high end estimate, this value was considered appropriate as seeds may be treated for several days and several types of seed may be treated. Cancer risks are below 1.0×10^{-5} and not of concern.

Even though it was assumed that closed cab tractors were used to generate the planting data in the GAUCHO 480 SC study, and closed cabs were used in the canola and corn planting studies, the calculated MOEs are considered high enough to cover off this uncertainty and closed cab tractors will not be required for planting seed treated with penflufen.

It should also be noted that mustard, sunflower and alfalfa dust off values may be higher than that for canola. As such, exposure from the surrogate study on canola may underestimate exposure to worker treating mustard, alfalfa and sunflower seeds. Even so, since the calculated MOEs are well above the targets, and cancer risk was low, exposure to workers planting these seeds with higher dust off potential is not expected to be of concern.

Exposure estimates for potato seed piece treater/planters wearing a work jacket over single layer (equivalent to coveralls over single layer) and gloves were based on a surrogate study measuring exposure to workers planting potato seed pieces treated with Moncereen DS 12.5. Note that the product used in the study was a powder formulation. Comparing exposure studies in the Pesticide Handlers Exposure Database (PHED) database, exposure estimates are higher when mixing/loading wettable powder formulations than when mixing/loading liquids. The exposure estimates from this study conducted with a powder formulation in coveralls over single layer and gloves can therefore cover off exposure estimates for treating with liquid formulation in single layer and gloves and planting with liquid formulation in coveralls over a single layer and gloves.

In this study a total of five farmers were monitored who handled about 15 kg to 30 kg product; the area treated varied from about 3.5 ha to 5.5 ha. The normalized exposure results found on the dosimeter clothing for the different operators did not vary very much. Given the small sample size (n=5), it was considered appropriate to use the 90^{th} percentile unit exposure values in the calculation of risk. The 90^{th} percentile values for dermal and combined inhalation exposure are 4.19 mg/kg a.i. handled and 0.145 mg/kg a.i. handled, respectively.

The exposure estimates and non-cancer risk of a small grower and a large grower treating/ planting potato seed pieces are presented in Appendix I, Table 13. Non-cancer risks for workers treating and planting is not of concern.

Small growers have fields smaller than 100 ha; therefore, if workers plant 20 ha/day, it would take five days to finish planting. Large growers have fields that are larger than 200 ha. If workers plant 40 ha/day, it would take five days to plant a 200 ha field. Cancer risk estimates for both small and large growers who treat and plant are presented in Appendix I, Table 14. The estimated cancer risk for all growers was above 1.0×10^{-5} and therefore not of concern. Therefore, for treater/planters, non-cancer and cancer risk is not of concern when wearing a single layer and gloves when treating and when wearing coveralls over single layer and gloves when planting.

Even though the exposure data are based on workers wearing coveralls and gloves, MOEs are considerably higher than the target and cancer risks are low for workers treating and planting potato seed pieces. In addition, the risk estimates for commercial treaters are acceptable without coveralls, and the planter risks are considered conservative as they are based on workers treating and planting. For these reasons, coveralls were not considered to be necessary for workers planting potato seed pieces treated with seed treatment products containing penflufen.

3.4.2.4 In-furrow potato seed pieces

Exposure estimates for in-furrow potato seed piece treatment were based on data from the PHED. PHED version 1.1 is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. With a few exceptions, the PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. To estimate exposure for workers applying seed treatment products containing penflufen in-furrow, appropriate subsets of A and B were created from the liquid mixer/loader and groundboom applicator database files of PHED. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part which is most appropriate to the distribution of data for that body part.

All non-cancer MOEs for workers treating potato seed pieces in-furrow were above the target MOE of 100 (Appendix I, Table 15) for workers wearing a single layer and gloves during mixing and loading and no gloves while applying. All cancer risk estimates were below 1.0×10^{-5} and are not of concern (Appendix I, Table 16).

3.4.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity, such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is penflufen. The HPLC-MS/MS data gathering/ enforcement analytical methods are valid for the quantitation of penflufen residues in crop and livestock matrices. The residues of penflufen are stable in potato tuber, head lettuce, dry bean seed, orange, wheat grain, wheat straw and sunflower seed for up to 26 months when stored in a freezer at ≤-18°C. The raw agricultural commodities corn, wheat and soybean were processed, but were not further analyzed due to the lack of quantifiable residues. Penflufen residues did not concentrate in the processed

commodities potato flakes or chips. Quantifiable residues are not expected to occur in livestock matrices with the current use pattern. Supervised residue trials conducted throughout the United States and Canada using end-use products containing penflufen in or on potatoes, beans, peas, soybeans, wheat, barley, sweet corn, field corn, sunflower, canola and cotton are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic non-cancer analysis: 100% crop treated, default processing factors (for animal commodities only), residues of penflufen in/on crops and animal commodities at ½ limit of quantitation (LOQ) values. The refined chronic dietary exposure from all supported penflufen food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1% of the ADI. Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to penflufen from food and water is 1.8% (0.000706 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for infants less than one year old at 5.5% (0.002182 mg/kg bw/day) of the ADI.

The refined chronic cancer risk assessment was conducted with the same criteria used for the chronic non-cancer assessment. The lifetime cancer risk from exposure to penflufen in food and water was estimated to be 1.8×10^{-6} for the general population, which is considered acceptable in view of the fact that the assessment was carried out with conservative criteria for estimates of food intake and drinking water, as detailed below:

- The main conservatism in the estimate of food intake is that the amount of potential crop to be treated was considered to be 100%. At this level, the lifetime cancer risk from exposure to penflufen in food (alone) was 1.9×10^{-7} for the general population, considerably below the level of concern.

- The points contributing to the conservatism of the drinking water values are three-fold. Mainly, the estimated environmental concentrations (EECs) used to determine drinking water estimates reflect standard conservative modeling practices, including maximum application rates and maximum yearly applications. The EEC values in the current assessment were based on in-furrow application to potato at the maximum rate of 160 g a.i./ha, whereas the present use mostly consists of seed treatments corresponding to rates of 10 g a.i./ha. This protective approach results in overestimation of risk, especially when based on chronic and lifetime exposure (e.g., cancer risk). Furthermore, using groundwater vs. surface water as the drinking water source contributes an additional level

of conservatism. In the current assessment, groundwater estimates were considered solely. For the majority of the Canadian population, the major source of drinking water is surface water; Prince Edward Island is the only province where the water source consists entirely of groundwater. Given that the surface water estimates were two orders of magnitude lower than groundwater estimates, analysis with groundwater estimates only results in a notably protective assessment. As well, the EEC values are based on a point of entry estimate, whereas the actual drinking water will most likely have lower residues than estimated given the further dilution of water as it reaches the drinking water sources.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following criteria were applied to the basic acute analysis: 100% crop treated, default processing factors, residues of penflufen in/on crops and animal commodities at MRL levels. The basic acute dietary exposure from all supported penflufen food uses was estimated to be 0.1% of the ARfD for the general population (95th percentile, deterministic). Aggregate exposure from food and water is considered acceptable and below PMRA's level of concern. Specifically, an acute dietary exposure of 1.2% to 5.3% of the ARfD was obtained for all population subgroups, with the highest exposed population subgroup all infants less than 1 year old.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for penflufen consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

MRLs are proposed as follows for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

Commodity	Recommended MRL (ppm)
Crop Subgroup 1C – Tuberous and Corm Vegetables Subgroup	0.01
Crop Group 6 – Legume Vegetables (Succulent or Dried) Group	0.01
Crop Group 15 – Cereal Grains	0.01
Crop Group 20 – Oilseeds Group	0.01
Eggs; fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; milk	0.01

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the chronic dietary risk estimates are summarized in Appendix I, Tables 1, 17 and 18.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties, penflufen is soluble in water, is not likely to volatilize from moist soil or water surfaces under field conditions, and is not likely to bioconcentrate or bioaccumulate in organisms.

The environmental fate data for penflufen are summarized in Appendix I, Table 19. Biotransformation is a major route of dissipation of penflufen in aerobic soil, but not in anaerobic soil. Penflufen is moderately persistent to persistent in soil, with two major transformation products observed under aerobic soil conditions. Photodegradation in soil was not studied, as the use of penflufen as a seed treatment and an in-furrow treatment will not leave penflufen exposed to sunlight. Laboratory studies on adsorption/desorption indicate that penflufen has potential to be moderately mobile. One of its transformation products has the potential to be mobile in a variety of soils. Penflufen was found to a soil depth of 60 cm in a field study in Idaho. At other field sites, however, penflufen and its transformation products could only be detected in the top 15 cm soil layer. No major transformation products of penflufen were identified in any of the field studies. The leaching potential of penflufen in the field is most probably offset by transformation processes, therefore, the potential for groundwater contamination is expected to be limited.

Hydrolysis, phototransformation, and biotransformation in aquatic systems are not expected to be important routes of penflufen transformation. Penflufen is stable to hydrolysis and phototransformation in water and is persistent in water/sediment systems. No major transformation products were detected in the aquatic studies. As penflufen is incorporated into the soil when used as a seed treatment or as an in-furrow treatment, the potential for penflufen to enter the aquatic environment through spray drift or surface runoff is expected to be limited.

Based on its physical-chemical properties and its intended use as a seed treatment and as an in-furrow treatment, penflufen is not expected to be found in air.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and

aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g., direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A risk assessment of penflufen and its representative end-use product PEN 240FS for terrestrial organisms was based upon an evaluation of toxicity data to earthworms (acute contact and reproduction), bees (acute oral and contact), predatory and/or parasitic invertebrates, birds (two acute oral, two dietary, and two chronic), mammals, (acute oral, dietary and chronic), and eleven species of terrestrial plants (seedling emergence and vegetative vigour). A summary of terrestrial toxicity data for penflufen is presented in Appendix I, Table 20. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with penflufen.

Earthworms and soil-dwelling arthropods

Penflufen is not acutely toxic to earthworms and soil mites up to the highest concentration tested (greater than 1000 mg a.i./kg soil and greater than 250 g a.i./ha, respectively). Earthworm (*Eisenia fetida*) survival was also not adversely affected by penflufen, however, the number of juvenile earthworms was reduced in the presence of penflufen. Penflufen did not adversely affect the fecundity of soil mites (*Hypoaspis aculeifer*). The screening level risk assessment was determined based on the EECs for the highest use rate scenario for penflufen on potatoes (160 g a.i./ha). The level of concern (LOC) was not exceeded for earthworms and soil mites (Appendix I, Table 21).

Bees (pollinators) and beneficial arthropods

No adverse effects were observed when bees were exposed to penflufen on an oral or contact basis. No mortality or adverse effects on fecundity were observed when the parasitic wasp (*Aphidius rhopalosiphi*) and predatory mite (*Typhlodromus pyri*) were exposed to penflufen on glass plates. As penflufen is incorporated into the soil when used as a seed treatment or in-furrow treatment and as it is not taken up from the treated seed to plant tissues or fluids, pollinators and beneficial arthropods are not expected to be exposed to penflufen residue. Pollinators and beneficial arthropods are, thus, not expected to be at risk from the application of penflufen from the Canadian use pattern.

Non-target plants

The effect of penflufen to non-target plants was determined through the exposure of the representative end-use product PEN 240FS through a seedling emergence and vegetative vigour assay using standard crop species. No significant adverse effects were observed in any plant species in either the seedling emergence or vegetative vigour assays. As penflufen is incorporated into the ground when used as a seed treatment or in-furrow treatment, exposure of non-target plants to penflufen through spray drift is considered to be negligible. Non-target plants are, thus, not expected to be at risk from the use of penflufen from the Canadian use pattern.

Birds and small wild mammals

No treatment-related mortalities or clinical effects were observed in the acute oral and dietary exposure of penflufen to various bird species including bobwhite quail (*Colinus virginianus*), mallard duck (*Anas platyrhynchos*), and canary (*Serinus canaria*). No adverse reproductive effects were observed in bobwhite quail, however, statistically significant reproductive effects (percent hatch versus live embryo and percent hatch versus eggs set) were observed on mallard ducks. The toxicity of penflufen to rats was used to determine risk to small terrestrial mammals. No mortality was observed during acute oral exposure of penflufen to rats. A significant reduction in litter size was observed in the two-generation reproduction study.

The screening level risk assessment was performed with canola seed as this seed type had the highest treatment rate on a g a.i./ha basis (the rate for potato seed pieces is higher, but potato seed pieces were not considered for the risk assessment because they are not a relevant food choice for birds and small wild mammals). The estimated dietary exposures and the toxicity endpoints were both expressed as the number of seeds consumed per day. The results of the risk assessment are presented in Appendix I, Table 22. The LOC was not exceeded for birds on an acute and dietary basis. The LOC was also not exceeded for large birds considering reproductive endpoints, but was exceeded for small and medium-sized birds (RQs of 1.9 and 1.5, respectively) based on endpoints for effects on reproduction. The LOC was not exceeded for small wild mammals based on potential acute, dietary or chronic exposures.

Because the screening level reproductive risk just marginally exceeds the LOC for small and medium sized birds, the avian reproductive risk from the use of penflufen as a seed treatment and in-furrow treatment is considered to be negligible. This is further supported by the conservative nature of the risk assessment where it is assumed that 100% of the diet is comprised of treated seed and parameters, such as availability of treated seeds and feeding preferences, which are not considered in the screening level assessment, would reduce the potential for birds to feed on the treated seeds and, thus, reducing the LOC. This is particularly true when considering feeding preference, as canola seeds may not be the preferred choice for birds due to their bitter taste. More importantly, since the level of concern for avian risk was not exceeded on an acute, dietary and reproductive basis for seeds other than canola seed, a reproductive risk to small and medium-sized birds from exposure to penflufen is not expected.

4.2.2 Risks to Aquatic Organisms

A risk assessment of penflufen and its representative end-use product PEN 240FS to freshwater aquatic organisms was based upon the evaluation of toxicity data on penflufen to *Daphnia magna* (acute and chronic), freshwater midge (chronic), four acute fish species for acute and one fish species for chronic effects, one algal (acute) and one vascular plant species (acute), and amphibian (using fish as surrogate data). For marine/estuarine organisms, the risk assessment was based on the evaluation of toxicity data on penflufen to two marine/estuarine invertebrate species (acute) and one estuarine fish species (acute). A summary of the freshwater and marine/estuarine toxicity data for penflufen is presented in Appendix I, Table 20. For the assessment of risk, toxicity endpoints from the most sensitive species was used as surrogates for the wide range of species that can be potentially exposed following treatment with penflufen.

The potential for spray drift and over-land run-off of penflufen to the aquatic environment is limited based on its registered use as a seed and in-furrow treatments. Nevertheless, the potential for adverse effects on aquatic organisms was assessed based on EECs from the direct application of the in-furrow application rate of penflufen (105.6 g a.i./ha) to water. The result of the screening level risk assessment for aquatic organisms is presented in Appendix I, Table 23.

Freshwater invertebrates

Acute exposure of *Daphnia magna* and crayfish (*Procambarus clarkia*) to penflufen did not result in significant mortality when compared to the respective control groups, however, acute exposure of *D. magna* to PEN 240FS resulted in significant mortality in the highest test concentration. No chronic adverse effects were observed in *D. magna*, however, freshwater midge growth was adversely affected by penflufen. The screening level risk assessment shows that the LOC was not exceeded for either acute or chronic exposures to freshwater invertebrates.

Freshwater fish and amphibians

The toxicity of penflufen to four species of fish rainbow trout, bluegill sunfish, fathead minnow and common carp) was assessed for acute exposure (while toxicity from chronic exposure was assessed using results from studies on fathead minnow. Penflufen was acutely toxic to all four

fish species in the range of concentrations tested (Appendix I, Table 20). Chronic exposure of penflufen to fathead minnow resulted in significant reductions in survival and several growth parameters when compared to the corresponding controls. The screening level risk assessment was performed with the common carp (acute) and fathead minnow (chronic). The LOC to exposure to penflufen was marginally exceeded for the acute (RQ = 1.5), but was not exceeded for chronic exposure to fish (Appendix I, Table 23). A refined Tier I assessment based on over-land run-off of penflufen into a receiving water body was conducted for acute exposure for fish. The LOC was not exceeded for acute exposure to fish in the refined risk assessment (Appendix I, Table 24).

The risk to aquatic life stages of amphibians was assessed using fish toxicity values as surrogate endpoints. Acute risk was based on results from the acute common carp, while chronic risk was based on the results from fathead minnow studies. The amphibian screening level risk quotients for both acute and chronic exposure to penflufen exceeded the LOC (Appendix I, Table 23). The risk quotients from the refined Tier I risk assessment for amphibians, however, did not exceed the LOC for both acute and chronic exposure (Appendix I, Table 24).

Freshwater algae and vascular plants

No adverse effects were observed when green algae (*Pseudokirchneriella subcapitata*) and duckweed (*Lemna gibba*) were exposed to penflufen on an acute basis. The screening level LOC was not exceeded for green algae and duckweed (Appendix I, Table 23).

Marine/estuarine species

Penflufen was acutely toxic to mysid shrimp (*Americamysis bahia*), Eastern oyster (*Crassostrea virginica*) and sheepshead minnow (*Cyprinodon variegates*) in the range of concentrations tested. The screening LOC was, however, not exceeded for any marine/estuarine species tested (Appendix I, Table 23).

No freshwater or marine/estuarine aquatic species identified as being at risk at the screening level were found to be at risk from the refined Tier I assessment for over-land run-off sources (Appendix I, Table 24).

4.2.3 Incident reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a time frame. Information on the reporting of incidents can be found on the Pesticides & Pest Management portion of the Health Canada's website. Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System. As of November 25th 2011, no environmental incident reports were found for penflufen.

5.0 Value

5.1 Effectiveness Against Pests

PEN 240FS and PENRED 240FS

The applicant presented evidence in the form of field and laboratory trials conducted in Canadian provinces and European locations that were deemed acceptable for review. In total, 94 field trials and 23 laboratory trials were submitted for evaluation. Thirty-one of the 33 proposed claims were conditionally or fully supported based on the adequate levels of protection achieved with PEN 240FS at the proposed rates.

PENPRO 118FS

In the three trials conducted on seed-borne *Rhizoctonia solani* under low to high disease pressure, PENPRO 118FS (2 g penflufen + 0.36 g prothioconazole/100 kg seed) and PEN 240FS (2 g penflufen/100 kg seed) were statistically equivalent with regard to plant emergence, incidence and severity of stem and stolon *Rhizoctonia*, incidence and severity of tuber *Rhizoctonia* and marketable yield. In two of three trials, a tank-mix of PEN 240FS (2 g penflufen/100 kg seed) and Redigo 100FS (0.36 g prothioconazole/100 kg seed) provided numerically or significantly better control of potato silver scurf than the commercial standard Maxim. PENPRO118FS or a tank-mix of PEN 240 FS and Redigo 100FS also provided consistent control of fusarium dry rot (87-99% disease reduction) in five of eight trials.

Based on the supported uses for PEN 240FS, the equivalence of performance observed between PEN 240FS and PENPRO 118FS, and the conclusive efficacy data on fusarium tuber rot, the use of PENPRO 118FS at the proposed rate is supported for control of black scurf, silver scurf and fusarium tuber rot.

PENCLO 273.5FS

Considering that 1) the use of PEN 240FS at 2 g penflufen/100 kg seed for control of the proposed diseases was supported in a related submission, and 2) PENCLO 273.5FS is also proposed for use at 2 g penflufen/100 kg seed, it is likely that both products will provide comparable efficacy against black scurf, stem and stolon canker, and silver scurf.

In one trial on seed-borne *Rhizoctonia solani*, a pre-mix containing penflufen (2 g a.i./100 kg seed) and chlothianidin (12.5 g a.i./100 kg seed) provided similar levels of control as PEN 240FS at the 2 g a.i. rate with regard to plant emergence, incidence and severity of stem and stolon *Rhizoctonia* as well as incidence and severity of tuber *Rhizoctonia* under moderate disease pressure. In three trials on seed-borne *Rhizoctonia solani*, PENCLO 273.5FS, a corresponding tank-mix of PEN 240FS and Titan ST (48% clothianidin), and the commercial standard Maxim all exhibited similar efficacy.

Based on the supported uses for PEN 240FS and the equivalence of performance observed between PEN 240FS and PENCLO 273.5FS, the use of PENCLO 273.5FS at the proposed rate is supported for control of black scurf, stem and stolon canker, and silver scurf. The addition of clothianidin in the pre-mix will result in an increased scope of controlled pests.

PENTRI 308FS

The applicant presented evidence in the form of field and laboratory trials conducted in Canadian provinces that were deemed acceptable for further review. In total, 29 field trials and 10 laboratory trials were submitted for evaluation. Twelve of the 14 proposed claims were conditionally or fully supported based on the adequate levels of protection achieved with PENTRI 308FS at the proposed rates.

PENCLOTRIME 310.68FS

In total, 19 field trials conducted in Canadian provinces and 9 laboratory trials were submitted for evaluation. Nine of the 14 proposed claims on canola, rapeseed and mustard (oilseed and condiment) were conditionally or fully supported based on the adequate levels of protection achieved with PENCLOTRIME 310.68FS.

PENPROME 177FS

In total, 57 field trials conducted in Canadian provinces and European locations as well as 15 laboratory trials were submitted for evaluation. Forty-four of the 46 proposed claims were conditionally or fully supported based on 1) the adequate levels of protection achieved with PENPROME 177FS, or 2) the extrapolation from a related prothioconazole-containing product registered at the same prothioconazole rate.

5.2 Tank-mixtures

Several tank-mixtures were proposed for the purpose of increasing the spectrum of controlled diseases or insects. Tank-mixtures were supported based on a lack of antagonism in efficacy trials.

5.3 Adverse effects

Overall, no issues were identified with regard to seed safety or crop tolerance in the efficacy field trials, tolerance field trials, laboratory germination tests and Iowa cold tests. Halo-like markings typical of neonicotinoids were observed in some trials testing PENCLOTRIME 310.68FS, but were not considered as major crop tolerance issues based on statistical similarities with the untreated control with regard to yield, seedling emergence, seedling vigour, canopy closure and percentages of germination, abnormal seedlings and dead seeds.

5.4 Economics

No market analysis was performed for this submission.

5.5 Sustainability

5.5.1 Survey of Alternatives

Refer to Appendix I, Table 25 for a summary of the active ingredients currently registered for the uses supported with the penflufen-containing products.

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

In several efficacy trials, penflufen was tank-mixed or pre-mixed with different insecticide (imidacloprid, clothianidin) and fungicide (metalaxyl, prothioconazole, trifloxystrobin) seed treatments without any substantial adverse effects, which is indicative of the compatibility of this active ingredient with conventional products and current production practices.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

According to the Fungicide Resistance Action Committee, carboxamides such as penflufen present a medium to high risk of resistance development. Penflufen-containing products are to be applied preventatively to the seeds, which minimizes the selection pressure on low risk seed-borne and soil-borne pathogens, as opposed to frequent foliar applications. Rotational products with different modes of action are registered for most proposed uses. The pre-mix fungicides PENPRO 118FS, PENTRI 308FS, PENCLOTRIME 310.68FS and PENPROME 177FS contain a combination of actives for effective resistance management.

PEN 240FS, PENRED 240FS, PENPRO 118FS, PENCLO 273.5FS, PENTRI 308FS, PENCLOTRIME 310.68FS and PENPROME 177FS fungicide labels include the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

5.5.4 Contribution to Risk Reduction and Sustainability

Penflufen represents an effective disease management tool and an additional rotational fungicide to prevent resistance development. For example, the use of PENPRO 118FS would reduce the selection pressure resulting from seed and post-harvest applications of fludioxonil- and azoxystrobin-containing products for the management of potato silver scurf. Penflufen products are also compatible for tank-mixing with certain insecticide and fungicide seed treatments on specific crops.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, penflufen and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Penflufen does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 26 for comparison with Track 1 criteria.

- Penflufen is hydroxylated and oxidized to form the two major transformation products. These resulting transformation products are more soluble in water than penflufen therefore the log K_{ow} value is expected to be lower than the parent. As such, the transformation products do not meet the Track 1 criteria

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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5 DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

8 DIR2006-02, PMRA Formulants Policy.

- All of the proposed end-use products contain low levels of 2,3,7,8-substituted PCDDs and PCDFs which are TSMP Track I substances. These are being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP.

- No other formulants or contaminants of health or environmental concern identified in the *Canada Gazette* are present in the proposed end-use products.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for penflufen is adequate to define the majority of toxic effects that may result from exposure. Penflufen is not considered to be a neurotoxicant. There was a low level of concern for effects on the immune system. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Penflufen is not genotoxic and there was no evidence of carcinogenicity in mice after longer-term dosing. However, tumours seen in rats were considered relevant for risk assessment. In short-term and chronic studies on laboratory animals, the target organs were the liver, thyroid, hematopoietic system, kidneys and adrenals. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Workers treating seed with PEN 240FS, PENRED 240FS, PENPRO 118FS, PENCLO 273.5FS, PENCLOTRIME 310.68FS, PENPROME 177FS and PENTRI 308FS and workers planting treated seed are not expected to be exposed to levels of penflufen or its coformulants that will result in an risks of concern when these products are used according to label directions. The personal protective equipment on the product labels is adequate to protect workers.

The nature of the residue in plants and animals is adequately understood. The residue definition is penflufen in plant products and in animal matrices. The proposed use of penflufen on cereal grains, oilseeds, legume vegetables, potato and alfalfa does not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs to protect human health. The PMRA recommends that the following MRLs be specified for residues of penflufen:

[9] DIR2006-02, PMRA Formulants Policy.

Commodity	Recommended MRL (ppm)
Crop Subgroup 1C – Tuberous and Corm Vegetables Subgroup	0.01
Crop Group 6 – Legume Vegetables (Succulent or Dried) Group	0.01
Crop Group 15 – Cereal Grains	0.01
Crop Group 20 – Oilseeds Group	0.01
Eggs; fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; milk	0.01

7.2 Environmental Risk

Penflufen is moderately persistent to persistent in most soils and aquatic systems. Penflufen has moderate to low potential to leach into ground water. As penflufen is used as a seed treatment and as an in-furrow treatment, penflufen is not expected to run-off into surface water. The risk assessment indicates that bees and beneficial arthropods, and non-target terrestrial plants are unlikely to be exposed to penflufen residue. Penflufen does not pose a risk to non-target aquatic organisms and treated seeds are unlikely to be consumed in sufficient quantities to cause adverse effects to wild birds and small wild mammals.

7.3 Value

Refer to Appendix I, Table 27 for a summary of the supported uses for each penflufen-containing product.

7.4 Unsupported Uses

The submitted efficacy data do not support the following claims:

Product(s)	Unsupported claim(s)
PEN 240FS and PENRED 240FS	Control of seed rot / pre-emergence damping-off caused by *Rhizoctonia solani* on sunflower and safflower. Suppression of seed-borne *Cochliobolus sativus* on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale
PENTRI 308FS	Suppression of seed-borne anthracnose (*Anthracnose* spp.) and ascochyta blight (*Ascochyta* spp.) on legume vegetables
PENCLOTRIME 310.68FS	Seedling blight caused by *Rhizoctonia solani* and *Fusarium* spp. on canola, rapeseed, mustard (oilseed and condiment) Seed-borne *Alternaria* spp. and blackleg (*Phoma lingam*) on canola, rapeseed, mustard (oilseed and condiment)
PENPROME 177FS	Root rot caused by seed-borne *Fusarium* spp. on corn (field, sweet, popcorn)

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of the technical product PENFLUFEN TC and the associated end-use products PEN 240FS, PENRED 240FS, PENPRO 118FS, PENPROME 177FS and PENTRI 308FS, containing the fungicidal active ingredient penflufen, for control of various seed-, seedling- and soil-borne diseases on oilseed and cereal grain crops, legume vegetables, alfalfa and potatoes.

It should be noted that, although full registration is proposed for the end-use product PENPROME 177FS, the PMRA is proposing conditional registration for the use of PENPROME 177FS on small grains due to the registration status of this use for the precedent prothioconazole seed-treatment product, JAU 6476 100 FS Seed Treatment Fungicide (Registration Number 30101).

The PMRA, under the authority of the *Pest Control Products Act* and Regulations, will be granting conditional registration for the sale and use of the end-use products PENCLO 273.5FS and PENCLOTRIME 310.68FS due to the registration status of the precedent clothianidin seed-treatment products, Titan ST Insecticide (Registration Number 27449) and Prosper FX Flowable Insecticide and Fungicide Seed Treatment (Registration Number 29159).

An evaluation of available scientific information found that, under the approved conditions of use, the proposed penflufen products have value and do not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	microgram(s)
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ALT	alkaline transaminase
AP	alkaline phosphatase
ARfD	acute reference dose
AST	aspartate transaminase
AUC	area under the curve
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BROD	benzyloxyresorufin-O-dealkylase
bw	body weight
BWG	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Act
cm	centimetres
C_{max}	maximum plasma concentration
d	day(s)
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	expected environmental concentration
ELS	early life stage
F	fumigant
F1	first generation
F2	second generation
FC	food consumption
FDA	Food and Drugs Act
FIR	food ingestion rate
g	gram(s)
GD	gestation day
GGT	gamma glutamyl transferase
GIT	gastrointestinal tract
h	hour(s)
ha	hectare(s)
HD	high dose
HDPE	high-density polyethylene
HDT	highest dose tested
HPLC	high performance liquid chromatography
IBC	intermediate bulk container
IUPAC	International Union of Pure and Applied Chemistry

kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	lethal concentration to 50%
LD	lactation day
LD_{50}	lethal dose to 50%
LLMV	lower limit of method validation
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate to 50%
MAS	maximum average score for 24, 48 and 72 hours
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre (s)
MLA	mixer/ loader/ applicator
MOE	margin of exposure
mol	mole(s)
MRL	maximum residue limit
MS	mass spectrometry
n/a	not applicable
NAFTA	North American Free Trade Agreement
NC	Not classified
NK	natural killer
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
NZW	New Zealand white
OC	organic carbon content
P	parental generation
Pa	Pascal(s)
PBI	plantback interval
PCDD	polychlorinated dibenzodioxins
PCDF	polychlorinated dibenzofurans
PCPA	Pest Control Product Act
PFC	plaque forming cells
PHED	Pesticide Handlers Exposure Database (PHED)
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PROD	pentoxyresorufin O-dealkylase

q_1*	cancer potency factor
RAC	raw agricultural commodity
rel	relative
RQ	risk quotient
sac	sacrifice
SC	soluble concentrate
SDHI	succinate dehydrogenase inhibitor
SOHD	single oral high dose
SOLD	single oral low dose
$t_{1/2}$	half-life
t_{max}	time to maximum plasma concentration
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Methods for residue analysis

Matrix	Method ID	Analyte(s)	Method Type	LOQ	Commodity	Reference
Plant	EL-002-P09-01/02/03	Penflufen	HPLC-MS/MS	0.01 ppm	potato tuber, carrot root and leaf, lettuce, barley forage and grain, dried bean, sunflower seed, orange	1885932 1885878
				0.05 ppm	barley straw	
Animal	EL-003-A10-01	Penflufen	HPLC-MS/MS	0.01 ppm	muscle, fat, liver, kidney, eggs, milk	1871604
Soil	01153	Penflufen	HPLC-MS/MS	5 µg/kg	n/a	1885920
Soil or sediment	01035	Penflufen BYF14182-3-hydroxybutyl BYF14182-pyrazolyl-AAP	HPLC-MS/MS	5 µg/kg	n/a	1886146 1886113 1984250
Water	EL-001-W08-02	Penflufen BYF14182-3-hydroxybutyl BYF14182-pyrazolyl-AAP	HPLC-MS/MS	0.1 µg/L	n/a	1885918 1886105 1886111

Table 2 Toxicokinetics and metabolism of penflufen

Study Results	Reference
The metabolism and toxicokinetics of penflufen were investigated in groups of 4 to 9 male and/or female Wistar rats (Hsd/Cpb: WU) following gavage administration of [Phenyl-^{14}C] penflufen and [Pyrazole-3-^{14}C] penflufen. The distribution of each radiolabelled penflufen was also assessed by quantitative whole-body autoradiography. **Dosing**: Single oral low dose (SOLD) = 2 mg/kg bw or 5 mg/kg bw. Single oral high dose (SOHD) = 200 mg/kg bw. Autoradiography dosing: SOLD = 5 mg/kg bw. Vehicle: 0.5% aqueous Tragacanth solution.	1885890 1885901 1886187 1886188 1885887
Absorption and excretion: Penflufen was almost completely absorbed (91% of administered dose (AD)) based on the recoveries of radioactivity in the bile, urine and body excluding the gastro-intestinal tract (GIT) from the SOLD experiment in males. The majority of excretion occurred within the first 24 hours and was nearly complete after 72 hours in both sexes. The predominant route of elimination in male rats was via the feces (59.6-66.8% of the AD). The urinary excretion accounted for 26.1-33.6% of the AD in males. In low dose females, approximately equal amount of radioactivity was detected in both the feces (45.6-61.0% of the AD) and urine (47.3-59.4% of the AD). Biliary elimination was measured in SOLD male rats and accounted for 70% of the AD over 48 hours post dosing. The overall recovery of administered radioactivity (urine, feces, organs and tissues, GIT and/or bile) at 72 hours post dosing ranged from 93.9-97.2% of the AD in both sexes. It was reported that <0.1% of the AD was measured in expired air of both sexes.	

Study Results	Reference
Distribution: Plasma toxicokinetic data showed that times to maximum plasma concentrations (t_{max}) were reached within 0.67 hours in males and 1 hour in females in SOLD animals and 1.5 hours in SOHD male rats, indicating rapid absorption of BYF 14182. The maximum plasma concentrations (C_{max}) were similar between SOLD males (0.59-0.74 µg/mL) and females (0.75 µg/mL) and the C_{max} was 19.19 µg/mL in SOHD males. The plasma concentrations declined to ≤1% and to 3.7% of the C_{max} within 72 hours post dosing in SOLD and SOHD animals, respectively. The $AUC_{0-\infty}$ value for females (3.6 mg/L·h) was ~1.5-fold higher than males (2.4-2.5 mg/L·h), suggesting a higher systemic exposure for female rats. The $t_{1/2}$ of elimination was similar in both sexes (males = 23.1-23.6 hours; females = 20.4 hours).	
The distribution pattern of radioactivity was similar between sexes. The maximum total radioactive residues (TRR) were reached for all organs and tissues at 1 hour post dosing and a similar distribution was observed throughout the experimental period. The highest TRRs were detected in the liver, erythrocytes and the kidneys of both sexes. High radioactivity levels were also observed in the myocardium, adrenals and Harderian gland of male rats. In females, brown fat, myocardium, pancreas, most glandular organs (e.g., adrenals, thyroid, Harderian gland), ovary and uterus showed a higher TRR than the blood. All tissue concentrations declined significantly after 24 hours and at 168 hours, the radioactivity in all organs and tissues was low or below the limit of quantification. Under the conditions of these studies, there was no evidence of bioaccumulation in either sex. These results agree with the quantitative whole body autoradiography studies.	
Metabolism: Penflufen was extensively metabolized. There were no significant differences in metabolic pathways between dose groups and sexes, however sex-specific quantitative differences in the pattern of metabolites were observed (e.g., higher amount (~3.6-fold) of desmethyl-dihydroxy-ketone metabolite was detected in females than in males). The parent compound was detected in low amount only in feces representing 0.03-1.25% of the AD in low dose animals and 1.79% of the AD in high dose rats. The majority of metabolites (58-94% of the AD) were identified. The major metabolic routes were demethylation of the pyrazole ring or hydroxylation of the side chain of the phenyl ring, the position 4' of the phenyl ring and the methyl group in position 3 of the pyrazole ring resulting in trihydroxy, dihydroxy and monohydroxy compounds. The hydroxylation of the position 3 of the alkyl side chain led to the intermediate BYF 14182-3-hydroxy-butyl. This metabolite was detected only in the bile at a very low amount, but was shown to be a key systemic intermediate in the metabolism of penflufen, as the toxicokinetic and metabolic behaviours of penflufen and BYF 14182-3-hydroxy-butyl were similar (PMRA # 1885897). Further oxidation of the hydroxyl groups led to keto or carboxylic acid compounds. Cleavage of the alkyl side chain and further oxidation, and cleavage of the carboxamide bond or N-phenyl bond resulted in other minor metabolites. BYF 14182-3-hydroxy-butyl and BYF 14182-pyrazolyl-AAP (not present in the rat metabolism studies) were identified as major soil metabolites.	

Table 3 Genotoxic potential of penflufen metabolites

Study Type	Study Results	Reference
BYF 14182-3-hydroxy-butyl		
Gene mutations in bacteria (Ames test)	**Negative** Tested up to limit and insoluble concentrations.	1886019
Chromosome aberrations *in vitro*	**Negative** Tested up to cytotoxic concentrations.	1886018
Gene mutations in mammalian cells *in vitro*	**Negative** Tested up to limit and insoluble concentrations.	1886020
BYF 14182-pyrazolyl-AAP		
Gene mutations in bacteria (Ames test)	**Negative** Tested up to limit and insoluble concentrations.	1886026
Chromosome aberrations *in vitro*	**Negative** Tested up to cytotoxic and insoluble concentrations.	1886025
Gene mutations in mammalian cells *in vitro*	**Negative** Tested up to limit of solubility in the solvent (44 µg/mL). Tested up to insoluble concentrations without S9.	1886024

Table 4 Toxicity profile of technical penflufen

Study Type	Animal	Study Results [a]	Reference
Oral (acute toxic class method)	Wistar rats	**Low Toxicity** Female LD_{50} > 5000 mg/kg bw	1885952
Dermal	Wistar rats	**Low Toxicity** LD_{50} > 2000 mg/kg bw	1885950
Inhalation (nose only)	Wistar rats	**Low Toxicity** LD_{50} > 2.022 mg/L	1885947
Skin irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/8	1885949
Eye irritation	NZW rabbits	**Minimally irritating** MAS (24, 48 and 72 h) = 2.2/110 *Conjunctival discharge scores were not provided. A score of "3" was used for conjunctival discharge when both conjunctival redness and chemosis were noted at a specific time-point.	1885948
Skin sensitization (maximization test of Magnusson and Kligman)	Hartley guinea pigs	**Not a skin sensitizer** 1st challenge: 5/20 (grade 1) at 24 h, 4/20 (grade 1) at 48 h 2nd challenge: 2/20 (grade 1) at 24 h, 0/20 at 48 h	1885941

Study Type	Animal	Study Results [a]	Reference
28-day oral toxicity (diet); non-guideline	C57BL/6J mice	Supplementary **≥ 26/31 mg/kg bw/day:** Adaptive effect: ↑ ALT **≥ 632/741 mg/kg bw/day:** ↓ cholesterol, ↑ AP, ↑ liver weight; ↓ total protein (♀) **1274/1585 mg/kg bw/day:** Enlarged liver, minimal diffuse centrilobular hepatocellular hypertrophy; ↑ severity of hepatocellular microvacuolation No hematological examination was conducted. Several clinical chemistry parameters were not measured and several organs were not examined microscopically and/or weighed.	1885964
90-day oral toxicity (diet); non-guideline	C57BL/6J mice	NOAEL = 26.9/31.5 mg/kg bw/day LOAEL = 638/757 mg/kg bw/day **≥ 638/757 mg/kg bw/day:** ↓ cholesterol Adaptive effects: ↑ liver weight, enlarged liver, diffuse centrilobular hepatocellular hypertrophy No ophthalmoscopic or hematological examinations, ovaries were not weighed, and several clinical chemistry parameters (sodium, potassium, glucose and creatinine levels) were not measured.	1885943
28-day oral toxicity; non-guideline	Wistar rats	Supplementary **≥ 154/169 mg/kg bw/day:** ↓ overall BWG, ↓ overall FC, ↑ cholesterol, ↓ AP (♀; non- adverse) Adaptive effects: ↑ total P-450, ↑ BROD, ↑ PROD; ↑ liver weight (♂) **560/648 mg/kg bw/day:** ↓ bilirubin, ↓ AST, ↓ ALT; ↑ cholesterol, ↑ severity of hyaline droplet nephropathy (♂); ↓ BW from Days 8-28, ↓ leucocyte count, ↓ neutrophil count, ↓ lymphocyte count, ↓ spleen weight (♀) Adaptive effects: ↑ liver weight, enlarged liver, centrilobular hepatocyte hypertrophy; prominent lobulation of the liver, slight microfoci of inflammation in the liver (♀)	1885958
90-day oral toxicity	Wistar rats	NOAEL = 9.5/11.4 mg/kg bw/day LOAEL = 457/492 mg/kg bw/day **457/492 mg/kg bw/day:** ↑ cholesterol, ↑ globulin, ↓ AST, ↑ liver weight, diffuse centrilobular hepatocellular hypertrophy, enlarged liver, dark liver; prominent lobulation in the liver, ↓ thymus weight, diffuse follicular cell hypertrophy of the thyroid with ↑ severity, colloid alteration in the thyroid, hyaline droplet nephropathy (♂); ↓ BW, ↓ overall BWG, ↓ terminal BW, ↓ FC, ↓ bilirubin, ↑ GGT, ↓ albumin/globulin ratio, ↓ ALT (♀)	1885944
90-day oral toxicity; non-guideline	Wistar rats	NOAEL = 9.3/11.4 mg/kg bw/day LOAEL = 228/260 mg/kg bw/day **228/260 mg/kg bw/day:** ↓ bilirubin, ↑ liver weight, diffuse centrilobular hepatocellular hypertrophy, ↑ thyroid weight; ↑ cholesterol, ↓ AST, ↓ ALT, hyaline droplet nephropathy (♂); ↓ BWG, ↓ AP (non-adverse), enlarged liver (♀)	1885946

Study Type	Animal	Study Results [a]	Reference
28-day oral toxicity; non-guideline	Beagle dogs	Supplementary **≥ 49/52 mg/kg bw/day:** prominent C-cell area in the thyroid **≥ 244/246 mg/kg bw/day:** ↑ prothrombin time, ↑ AP, ↑ GGT, diffuse centrilobular hepatocellular hypertrophy, decreased thyroid follicular diameter; diffuse follicular cell hypertrophy of the thyroid (♂) **759/895 mg/kg bw/day:** ↓ FC, ↓ cholesterol	1885961
90-day oral toxicity	Beagle dogs	NOAEL = 55.7/63.1 mg/kg bw/day LOAEL = 532/568 mg/kg bw/day **532/568 mg/kg bw/day:** ↑ prothrombin time, ↓ cholesterol, ↓ albumin, ↓ albumin/globulin ratio, ↑ GGT, ↑ AP, ↑ liver weight, diffuse panlobular hepatocellular hypertrophy, multifocal intrahepatocellular eosinophilic material, multifocal perilobular single cell death; ↓ FC at week 1, ↓ total protein, ↑ thyroid weight, ↑ adrenal weights, diffuse cortical hypertrophy/hyperplasia in the adrenal (♂); ↓ BW, ↓ overall BWG, ↓ terminal BW, ↓ overall FC, ↑ platelet count at week 12/13 (♀)	PMRA # 1886029
12-month oral toxicity	Beagle dogs	NOAEL = 32.0/37.9 mg/kg bw/day LOAEL = 357/425 mg/kg bw/day **32.0/37.9 mg/kg bw/day:** Adaptive effects: ↑ GGT (♀), ↑ liver weight (♀) **357/425 mg/kg bw/day:** ↓ FC at week 1, ↓ albumin, ↓ albumin/globulin ratio, ↓ calcium, ↓ phosphorus at week 52, ↓ cholesterol, ↑ liver weight, ↑ AP, ↑ GGT, panlobular hepatocellular hypertrophy, focal hepatocellular brown pigment, dark thyroid, diffuse follicular cell hypertrophy of the thyroid; ↑ prothrombin time at months 4&7, enlarged liver (♂); ↓ BW, ↓ overall BWG, ↓ terminal BW, focal/multifocal zona glomerulosa vacuolation of the adrenal (♀)	PMRA # 1885953
28-day dermal toxicity	Wistar rats	Systemic NOAEL = 1000 mg/kg bw/day Dermal irritation NOAEL = 1000 mg/kg bw/day Systemic and dermal irritation LOAELs = Not established **1000 mg/kg bw/day:** ↑ lymphocyte debris within the thymic cortices (♂; non-adverse)	1885904
18-month carcinogenicity study (diet)	C57BL/6J mice	NOAEL = 880 mg/kg bw/day in ♂, 182 mg/kg bw/day in ♀ LOAEL = Not established in ♂, 1101 mg/kg bw/day in ♀ **≥ 146/182 mg/kg bw/day:** Adaptive effect: Diffuse centrilobular hepatocellular hypertrophy and vacuolation (♀) **880/1101 mg/kg bw/day:** ♀: ↓ BWG, ↓ overall BWG, ↓ leucocyte counts, ↓ kidney weight, enlarged thyroid, follicular cell hyperplasia of the thyroid, unilateral fibrosis/atrophy of the kidneys, diffuse hepatocellular macrovacuolation-mainly periportal Adaptive effects: ↑ liver weight, enlarged liver; diffuse hepatocellular vacuolation (♂); pale liver (interim sac ♀)	1886039

Study Type	Animal	Study Results [a]	Reference
24-month oral toxicity (diet)	Wistar rats	NOAEL = 4.0/5.6 mg/kg bw/day LOAEL = 79/113 mg/kg bw/day **79/113 mg/kg bw/day:** ↓ AP (non-adverse), ↓ ALT, ↓ bilirubin, ↑ liver weight (interim sac), hepatocellular hypertrophy, hepatocellular macrovacuolation; ↓ BW, ↓ BWG, ↓ terminal BW, ↓ FC from weeks 13-104, ↑ cholesterol at months 4-12, enlarged liver, white focus in liver, focal hepatocellular brown pigment (♀) **Recovery groups**: All the adverse effects noted in treated animals following 52 week of treatment were either partially (↓ bilirubin HD ♂) or totally resolved. Neoplastic lesions: Histiocytic sarcomas (terminal sac), brain astrocytomas (terminal sac-unscheduled death only ♂); ovarian tubulostromal adenomas (terminal sac ♀)	1886044
One-generation dietary reproductive toxicity (diet); range finding study; non-guideline	Wistar rats	Supplementary *Parental Toxicity* **≥ 135/164 mg/kg bw/day:** ↑ liver weight; ↓ BW, ↓ BWG (no change at high dose), ↓ terminal BW (♀) **≥ 291/331 mg/kg bw/day:** ↑ FC, ↓ BW (♀) **494/669 mg/kg bw/day:** ↓ BW, ↓ BWG, ↓ terminal BW, ↓ FC, ↓ spleen weight (♂); ↑ FC (♀) *Offspring Toxicity* **≥ 331 mg/kg bw/day:** ↓ BW, ↓ BWG, ↓ litter size (no change at high dose), ↓ spleen weight **669 mg/kg bw/day:** ↓ brain weight, ↓ thymus weight *Reproductive Toxicity* **669 mg/kg bw/day:** reduced testes and epididymides size in 2 ♂ (co-housed ♀ were not pregnant) *Estrous cycling, sperm analysis, micropathology and pup sexual maturation were not performed.	1967879
2-generation dietary reproductive toxicity (diet)	Wistar rats	*Parental Toxicity* NOAEL = 64/76 mg/kg bw/day LOAEL = 252/294 mg/kg bw/day **252.2/294.5 mg/kg bw/day:** ↓ BW, ↓ BWG (P), ↑ BWG (F_1), alteration in FC, ↓ terminal BW, ↓ thymus weight; ↑ thyroid weight (♂) Adaptive effects: ↑ liver weight, liver hypertrophy *Offspring Toxicity* NOAEL = 76 mg/kg bw/day LOAEL = 293 mg/kg bw/day **293 mg/kg bw/day:** ↓ BW (LD 4-21), ↓ BWG (LD 0-21), delay in vaginal opening (F_1, F_2), delay in preputial separation (F_1, F_2), ↓ terminal BW, ↓ spleen weight, ↑ rel brain weight *Reproductive Toxicity* NOAEL = 75.9 mg/kg bw/day LOAEL = 293 mg/kg bw/day **293.4 mg/kg bw/day:** ↓ litter size at Day 0	1886198

Study Type	Animal	Study Results [a]	Reference
Oral developmental toxicity (gavage); range-finding study; non-guideline	Sprague-Dawley rats	Supplementary *Maternal Toxicity* **≥ 50 mg/kg bw/day:** ↓ BWG at 50 mg/kg bw/day (transient) Adaptive effect: ↑ liver weight **≥ 300 mg/kg bw/day:** ↓ BWG from GD 6-21 (with BW loss at GD 6-8), ↓ overall BWG, ↓ corrected BWG, ↓ FC **1000 mg/kg bw/day:** 1 ♀ sacrificed on GD 19 (soiling around the mouth on GD 17-19; soiled anogenital region on GD 18-19; ↓ motor activity on GD 19; BW loss and ↓ FC between GD 16-18) *Developmental Toxicity* **≥ 300 mg/kg bw/day:** ↓ fetal weight	1967878
Oral developmental toxicity (gavage)	Sprague-Dawley rats	*Maternal Toxicity* NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day No treatment-related effects on survival, clinical signs or caesarean section parameters. **≥ 100 mg/kg bw/day:** ↓ BWG (transient; non-adverse) Adaptive effect: Prominent lobulation of the liver **300 mg/kg bw/day:** ↓ BWG from GD 6-21 (with BW loss from GD 6-8), ↓ corrected BWG, ↓ FC from GD 6-12 Adaptive effect: ↑ liver weight *Developmental Toxicity* NOAEL = 300 mg/kg bw/day LOAEL = Not established No treatment-related external, visceral or skeletal malformations or variations.	1885956
Oral developmental toxicity (gavage); range-finding study; non-guideline	NZW rabbits	Supplementary *Maternal Toxicity* **≥ 300 mg/kg bw:** few and/or soft feces One dam sacrificed on GD 19 after abortion (BW loss from GD 16-18) One dam sacrificed on GD 25 (↓ BW from GD 12-24, ↓ FC from GD 20-24, no or few feces from GD 17-25, red traces were noted in cage tray on day of sacrifice, white foci on the gall bladder) **≥ 600 mg/kg bw:** hair loss The following findings were only observed at 600 mg/kg bw/day: ↓ BWG from GD 6-18, ↓ overall BWG, ↓ corrected BWG, ↓ FC from GD 6-18 **1000 mg/kg bw:** One dam sacrificed on GD 20 (↓ BW, ↓ FC, no or few feces prior to sacrifice, no urine on GD 15 and 20, hair loss on abdomen from GD 12-20, abnormal colored-green placentae, white foci on the gall bladder) One dam sacrificed on GD 24 after abortion (↓ BW from GD 12-22, ↓ FC from GD 12-24, few feces from GD 13-24, hair loss on abdomen from GD 16-24) *Developmental Toxicity* **≥ 300 mg/kg bw:** one abortion at 300 mg/kg bw/day **≥ 600 mg/kg bw:** ↓ fetal weight, ↑ % runt fetuses (both fetus and litter basis, only noted at 600 mg/kg bw/day) **1000 mg/kg bw:** ↓ live fetuses per litter, one abortion	1967877

Study Type	Animal	Study Results [a]	Reference
Oral developmental toxicity (gavage)	NZW rabbits	*Maternal Toxicity* NOAEL = 100 mg/kg bw/day LOAEL = 600 mg/kg bw/day No treatment-related effects on survival, clinical signs or caesarean section parameters. **100 mg/kg bw/day:** ↓ overall BWG from 6-29 (non-adverse) **600 mg/kg bw/day:** ↓ BWG from GD 8-22, ↓ overall BWG from GD 6-29, ↓ corrected BWG, ↓ FC from GD 6-22 1 HD ♀ sacrificed for humane reasons on GD 25 (few feces between GD 17-25; lost 640 g from GD 6-25; stopped eating at GD 14, no necropsy findings). Similar effects in range-finding study at similar doses. Adaptive effects: ↑ liver weight *Developmental Toxicity* NOAEL = 100 mg/kg bw/day LOAEL = 600 mg/kg bw/day **600 mg/kg bw/day:** ↓ fetal weight, incomplete ossification of the 5^{th}-6^{th} sternebrae	1885954
Acute neurotoxicity (gavage)	Wistar rats	NOAEL = 100 mg/kg bw in ♂, 50 mg/kg bw in ♀ LOAEL = 500 mg/kg bw in ♂, 100 mg/kg bw in ♀ **≥ 100 mg/kg bw:** ↓ motor activity at Day 0, ↓ locomotor activity at Day 0 (♀) **500 mg/kg bw:** Urine stain Days 0-2; yellow urine during handling, ↓ motor activity at Day 0, ↓ locomotor activity at Day 0 (♂); stiff-legged hindlimbs, ataxia, ↓ activity at Day 0, clear lacrimation at Day 0, ↓ body temperature at Day 0 (♀)	1885917
90-day neurotoxicity (diet)	Wistar rats	NOAEL = 126/156 mg/kg bw/day LOAEL = 516/609 mg/kg bw/day **126/156 mg/kg bw/day:** ↓ overall BWG (♀; non-adverse) Adaptive effect: ↑ liver weight **516/609 mg/kg bw/day:** ↓ BW, ↓ overall BWG, ↓ terminal BW, ↓ FC; ↓ motor activity from weeks 4-13, ↓ locomotor activity from weeks 4-13 (♀)	1885905
Gene mutations in bacteria (Ames test)		**Negative** Tested up to limit, insoluble and cytotoxic concentrations.	1885966
Gene mutations in bacteria (Ames test); new impurity profile (batch GELL 605-242-2)		**Negative** Tested up to limit and insoluble concentrations.	1886190
Chromosome aberrations *in vitro*		**Negative** Tested up to cytotoxic concentrations.	1885959
Chromosome aberrations *in vitro*; new impurity profile (batch GELL 605-242-2)		**Negative** Tested up to cytotoxic concentrations.	1886106
Gene mutations in mammalian cells *in vitro*		**Negative** Tested up to cytotoxic concentrations.	1885975

Study Type	Animal	Study Results [a]	Reference
Gene mutations in mammalian cells *in vitro*; new impurity profile (batch GELL 605-242-2)		**Negative** Tested up to cytotoxic concentrations.	1886104
Micronucleus assay *in vivo* (intraperitoneal injection)	NMRI mice	**Negative** Tested up to a limit dose. **250 mg/kg bw/day**: Clinical signs including apathy, roughened fur, weight loss, sternal recumbency, spasm, difficulty in breathing and slitted eyes.	1885960
30-day immunotoxicity (diet), PFC assay	Wistar rats	**Unacceptable** Based on absence of concurrent positive control, failure to report PFC/spleen and absence of NK cell activity assay. **≥ 82.6/104.5 mg/kg bw/day:** ↑ water intake (♂) **755.6/960.5 mg/kg bw/day:** ↓ BW, ↓ overall BWG, ↑ FC (associated with food spillage); ↑ water intake (♀)	1885969

[a] Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.

Table 5 Toxicity profile of penflufen end-use products

Study Type	Animal	Study Results [a]	Reference
PEN 240FS and PENRED 240FS			
Acute oral toxicity	Wistar rats	**Low toxicity** Female LD_{50} > 2000 mg/kg bw	1885273
Acute dermal toxicity	Wistar rats	**Low toxicity** LD_{50} > 2000 mg/kg bw	1885274
Acute inhalation toxicity (nose only)	Wistar rats	**Low toxicity** LC_{50} > 1.887 mg/L	1885275
Dermal irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/8 MIS = 0/8	1885276
Eye irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/110 MIS = 0/110	1885279
Dermal sensitization (local lymph node assay)	CBA/J mice	**Not a dermal sensitizer** Stimulation Index 25% = 0.9 50% = 0.9 100% = 0.8 Positive control = 3.8	1885280

Study Type	Animal	Study Results [a]	Reference
PENPRO 118FS			
Acute oral toxicity	Wistar rats	**Low toxicity** Female LD_{50} > 2000 mg/kg bw Clinical sign: Decreased motility; sign resolved within 2 hours	1885322
Acute dermal toxicity	Wistar rats	**Low toxicity** LD_{50} > 2000 mg/kg bw Clinical sign: Partial encrustation, partial red discoloration of the treated skin; signs resolved within 3 days	1885323
Acute inhalation toxicity (nose only)	Wistar rats	**Low toxicity** LC_{50} > 3.88 mg/L One death; attributed to lung edema	1885324
Dermal irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/8 MIS = 0/8 Clinical sign: red discoloration of the treated skin; signs resolved by Day 7 or 14	1885325
Eye irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/110 MIS = 1.33/110	1885326
Dermal sensitization (local lymph node assay)	CBA/J mice	**Not a dermal sensitizer** Stimulation Index 25% = 0.9 50% = 0.9 100% = 1.4 Positive control = 4.4	1885328
PENCLO 273.5FS			
Acute oral toxicity	Wistar rats	**Low toxicity** Female LD_{50} > 2000 mg/kg bw	1885681
Acute dermal toxicity	Wistar rats	**Low toxicity** LD_{50} > 2000 mg/kg bw Clinical sign: Partial encrustation, partial red discoloration of the treated skin; signs resolved within 2 days	1885682
Acute inhalation toxicity (nose only)	Wistar rats	**Low toxicity** LC_{50} > 2.75 mg/L Clinical signs: irregular breathing, piloerection, bradypnea, laboured breathing patterns, reduced motility, limp, miosis or high-legged gait; signs resolved by Day 4	1885683

Study Type	Animal	Study Results [a]	Reference
Dermal irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/8 MIS = 0/8	1885684
Eye irritation	NZW rabbits	**Minimally irritating** MAS (24, 48 and 72 h) = 1.33/110 MIS = 2.67/110	1885685
Dermal sensitization (local lymph node assay)	CBA/J mice	**Not a dermal sensitizer** Stimulation Index 10% = 1.7 25% = 1.4 50% = 1.8 100% = 2.0 Positive control = 8.0	1885686
PENCLOTRIME 310.68FS			
Acute oral toxicity	Wistar rats	**Low toxicity** Female LD_{50} > 2000 mg/kg bw	1885711
Acute dermal toxicity	Wistar rats	**Low toxicity** LD_{50} > 2000 mg/kg bw	1885712
Acute inhalation toxicity (nose only)	Wistar rats	**Low toxicity** LC_{50} > 2.25 mg/L Necropsy: blue discoloration of the lung and/or blue discoloration of the lung associated lymph nodes	1885713
Dermal irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/8 MIS = 0/8 Clinical sign: blue discoloration of the treated skin; sign resolved by Day 7 in one rabbit, but persisted through Day 14 in two rabbits	1885714
Eye irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/110 MIS = 2/110	1885715
Dermal sensitization (local lymph node assay)	CBA/J mice	**Not a dermal sensitizer** Stimulation Index 25% = 1.2 50% = 1.4 100% = 1.7 Positive control = 12.0	1885716
PENPROME 177FS			
Acute oral toxicity	Wistar rats	**Low toxicity** Female LD_{50} > 2000 mg/kg bw Clinical sign: decreased motility; sign resolved within 6 hours	1885743
Acute dermal toxicity	Wistar rats	**Low toxicity** LD_{50} > 2000 mg/kg bw	1885744

Study Type	Animal	Study Results [a]	Reference
Acute inhalation toxicity (nose only)	Wistar rats	**Low toxicity** LC_{50} > 2.20 mg/L Clinical sign: irregular breathing, breathing sounds, piloerection; signs resolved by Day 1 or Day 3	1885745
Dermal irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/8 MIS = 0/8	1885746
Eye irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/110 MIS = 2/110	1885748
Dermal sensitization (local lymph node assay)	CBA/J mice	**Not a dermal sensitizer** Stimulation Index 25% = 1.3 50% = 1.2 100% = 1.7 Positive control = 13.7	1885749
PENTRI 308FS			
Acute oral toxicity	Wistar rats	**Low toxicity** Female LD_{50} > 2000 mg/kg bw Clinical sign: decreased motility; sign resolved within 4 hours	1885808
Acute dermal toxicity	Wistar rats	**Low toxicity** LD_{50} > 2000 mg/kg bw Clinical sign: partial blue discoloration of the treated skin; sign resolved by Day 10	1885810
Acute inhalation toxicity (nose only)	Wistar rats	**Low toxicity** LC_{50} > 1.995 mg/L Necropsy: blue-grey discoloration of the lung, enlarged lung associated lymph nodes with blue-grey discoloration	1885813
Dermal irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/8 MIS = 0/8 Clinical sign: dark blue discoloration of the treated skin; sign was not completely cleared following 14 days	1885816
Eye irritation	NZW rabbits	**Non-irritating** MAS (24, 48 and 72 h) = 0/110 MIS = 2/110	1885818
Dermal sensitization (local lymph node assay)	CBA/J mice	**Not a dermal sensitizer** Stimulation Index 10% = 1.6 25% = 1.6 50% = 1.7 Positive control = 7.9	1885820

[a] Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.

Table 6 Toxicology endpoints for use in health risk assessment for penflufen

Exposure scenario	Study	Point of departure and endpoint	CAF[a] or target MOE
Acute dietary	Acute neurotoxicity rat study	NOAEL = 50 mg/kg bw; based on decreased motor and locomotor activity levels noted at Day 0 in females at the LOAEL of 100 mg/kg bw	100
	ARfD = 0.5 mg/kg bw		
Repeated dietary	24-Month rat combined chronic/carcinogenicity study	NOAEL = 4 mg/kg bw/day; based on decreased BW, BWG , FC, ALT activity, bilirubin levels, and increased cholesterol levels and liver weight associated with gross and histopathological findings observed at the LOAEL of 79 mg/kg bw/day	100
	ADI = 0.04 mg/kg bw/day		
Short-term and intermediate-term dermal	28-day dermal rat study	NOAEL = 1000 mg/kg bw/day (HDT)	100
Short-term and intermediate inhalation[b]	90-day dog study	NOAEL = 55.7 mg/kg bw/day; based on decreased BW, BWG, FC, cholesterol, albumin, albumin/globulin ratio and total protein levels, and increased platelet counts, prothrombin time, γ-glutamyl-transferase activity, alkaline phosphatase activity, thyroid weight, liver weight associated with histopathological findings, and adrenal weights with associated histopathology observed at the LOAEL of 532 mg/kg bw/day	100
Cancer	Ovarian tubulostromal adenomas, malignant brain astrocytomas and histiocytic sarcomas were observed in the 24-month rat combined chronic/carcinogenicity study. A q_1* value of 2.59×10^{-3} $(mg/kg\ bw/day)^{-1}$ derived from the ovarian tubulostromal adenomas was selected for cancer risk assessment.		

[a] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[b] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 7 Exposure & non-cancer risk estimates for workers treating seeds in commercial seed treatment facilities for workers wearing a single layer and gloves

Scenario	Unit exposure (µg/kg ai handled)		kg seed treated per day	App rate (kg ai/kg seed)	kg ai handled per day[b]	Exposure[c] (mg/kg bw/day)		MOE[d]	
	Dermal	Inhalation				Dermal	Inhalation	Dermal	Inhalation
Cereals									
Treating[a]	265.70	2.47	325 700	0.00005	16.3	0.0619	0.000575	16178	96843
Oilseeds, Alfalfa, Legumes and Corn (Worst Case Estimate)									
Treater/ Applicator	2184	6.94	325 700	0.00005	16.3	0.509	0.00162	1966	34467
Bagger/Sewer/ Stacker	115.5	8.9	325 700	0.00005	16.3	0.0269	0.00207	37182	26877
Cleanout[e] (single layer +gloves)	144.3	20.0	15 g ai/100 kg seed			0.0309	0.00429	32340	12997
Cleanout[e] (coveralls + gloves)	56.2	20.0	5 g ai/100 kg seed			0.0120	0.00207	83037	26877
Potato Seed Pieces									
Treating	291	11.5	290 400	0.00002	5.8	0.0241	0.000953	41474	58456
Cutting/ sorting	n/a	18.0	290 400	0.00002	5.8	n/a	0.00149	n/a	37347
Treating and cutting/ sorting[f]	291	18.0	290 400	0.00002	5.8	0.0241	0.00149	41474	37347

[a] 90th percentile unit exposure values from the GAUCHO 480 SC study.

[b] kg ai handled per day = kg seed treated per day × application rate (kg ai/kg seed)

[c] Exposure (mg/kg bw/day) = [Unit exposure (µg/kg ai handled per day) × kg ai handled per day] / [70 kg bw × 1000 µg/mg]

[d] Dermal NOAEL = 1000 mg/kg bw/day, target MOE= 100; inhalation NOAEL = 55.7 mg/kg bw/day, target MOE = 100

[e] For Cleanout personnel, unit exposures are normalized for application rate (the highest application rate proposed was used) therefore: Exposure (mg/kg bw/day) = [Unit exposure (µg ai/100 kg seed) × application rate (g ai/100 kg seed)] / [70 kg bw × 1000 µg/mg]

[f] The exposure from treating and cutting/sorting were combined since the treater may occasionally provide brief relief to a worker on the cutting/sorting line (dermal exposure for treating + inhalation exposure from cutting/sorting).

Table 8 Cancer risk assessment for commercial workers wearing a single layer and gloves

Scenario	Daily exposure (mg/kg bw/day)[a]	Days of exposure per year	LADD (mg/kg bw/day) [b]	Cancer risk[c]
Cereals				
Commercial treating	0.00447	60	3.91×10^{-4}	1.0×10^{-6}
Oilseeds, Alfalfa, Legumes, Corn				
Treater/applicator	0.0337	60	0.0030	7.6×10^{-6}
Bagger/sewer/stacker	0.00376	60	3.3×10^{-4}	8.5×10^{-7}
Cleanout personnel	0.00623	60	5.5×10^{-4}	1.4×10^{-6}
Potato Seed Pieces				
Treating	0.00250	30	1.1×10^{-4}	2.8×10^{-7}
Cutting/sorting	0.00149	30	6.5×10^{-5}	1.7×10^{-7}
Treating and cutting/sorting[d]	0.00256	30	1.1×10^{-4}	2.9×10^{-7}

[a] Daily exposure = (Dermal exposure × 6.3% dermal absorption) + Inhalation Exposure
[b] LADD (Lifetime average daily dose) = (Daily exposure × Days of exposure per year × 40 years of work) / (365 days per year × 75 year life expectancy)
[c] Based on a $q_1^* = 2.59\times10^{-3}$
[d] The exposure from treating and cutting/sorting were combined since the treater may occasionally provide brief relief to a worker on the cutting/sorting line (dermal exposure for treating + inhalation exposure from cutting/sorting).

Table 9 Exposure & risk estimates for penflufen for workers treating cereals, oilseeds, alfalfa, legumes and corn in on-farm seed treatment facilities and wearing a single layer and gloves

Scenario	Unit exposure (µg/kg ai handled)[a]		kg seed treated per day	App rate (kg ai/kg seed)	kg ai handled per day[b]	Exposure[c] (mg/kg bw/day)		MOE[d]	
	Dermal	Inhalation				Dermal	Inhalation	Dermal	Inhalation
Cereals	145.22	7.61	13600	0.00005	0.68	0.00141	0.0000739	708864	753459
Canola/Mustard	145.22	7.61	600	0.00015	0.09	0.000187	0.00000978	5355859	5692801
Oilseeds/Alfalfa	145.22	7.61	3600	0.00015	0.54	0.00112	0.0000587	892643	948800
Sunflower/ Safflower	145.22	7.61	3600	0.00005	0.18	0.00037	0.0000196	2677929	2846401
Legumes	145.22	7.61	20000	0.00005	1.0	0.00207	0.000109	482027	512352
Corn	145.22	7.61	1350	0.00005	0.068	0.000141	0.00000739	7088636	7534591

[a] Unit exposure values are from the GAUCHO 480 SC study.
[b] Kg ai handled per day = kg seed treated per day × application rate (kg ai/kg seed)
[c] Exposure (mg/kg bw/day) = [Unit exposure (µg/kg ai handled per day) × kg ai handled per day] / [70 kg bw × 1000 µg/mg]
[d] Dermal NOAEL = 1000 mg/kg bw/day, target MOE= 100; inhalation NOAEL = 55.7 mg/kg bw/day, target MOE = 100

Table 10 Cancer risk assessment for on-farm treaters wearing a single layer and gloves

Scenario	Daily exposure (mg/kg bw/day) [a]	Days of exposure per year	LADD (mg/kg bw/day) [b]	Cancer risk [c]
Cereals	0.000163	10	2.4×10^{-6}	6.2×10^{-9}
Canola/Mustard	0.0000216	10	3.2×10^{-7}	8.2×10^{-10}
Oilseeds/Alfalfa	0.000129	10	1.9×10^{-6}	4.8×10^{-9}
Sunflower/ Safflower	0.0000429	10	6.3×10^{-7}	1.6×10^{-9}
Legumes	0.000239	10	3.5×10^{-6}	9.0×10^{-9}
Corn	0.0000163	10	2.4×10^{-7}	6.2×10^{-10}

[a] Daily exposure = (Dermal exposure × 6.3% dermal absorption) + Inhalation Exposure
[b] LADD (Lifetime average daily dose) = (Daily exposure × Days of exposure per year × 40 years of work) / (365 days per year × 75 year life expectancy)
[c] Based on a $q_1^* = 2.59\times10^{-3}$

Table 11 Exposure and risk estimates for workers planting treated oilseeds, alfalfa, legumes and corn from bags

Scenario	Unit exposure (µg/kg ai handled)[1]		kg seed treated per day	App rate (kg ai/kg seed)	kg ai handled per day [2]	Exposure [3] (mg/kg bw/day)		MOE [4]	
	Dermal	Inhalation				Dermal	Inhalation	Dermal	Inhalation
Legumes	424.17	1.11	20000	0.00005	1.0	0.00606	0.0000159	165028	3512613
Oilseeds/ Alfalfa	424.17	1.11	3600	0.00015	0.54	0.00327	0.00000856	305608	6504838
Corn/ Sorghum	1803	82.83	1350	0.00005	0.068	0.00175	0.0000805	570944	692240
Sunflower/ Safflower	1803	82.83	3600	0.00005	0.18	0.00464	0.000213	215690	261513

[a] Unit exposure values for planters of treated legume, oilseed and alfalfa seed are from the canola planting study. Unit exposure values for planters of treated corn, sunflower and safflower seed are from the corn planting study.
[b] kg ai handled per day = kg seed treated per day × application rate (kg ai/kg seed)
[c] Exposure (mg/kg bw/day) = [Unit exposure (µg/kg ai handled per day) × kg ai handled per day] / [70 kg bw × 1000 µg/mg]
[d] Dermal NOAEL = 1000 mg/kg bw/day, target MOE= 100; inhalation NOAEL = 55.7 mg/kg bw/day, target MOE = 100

Table 12 Cancer risk assessment for planters wearing a single layer and gloves

Scenario	Daily exposure (mg/kg bw/day) [a]	Days of exposure per year	LADD (mg/kg bw/day) [b]	Cancer Risk[c]
Legumes	0.000398	10	5.8×10^{-6}	1.5×10^{-8}
Oilseeds/Alfalfa	0.000215	10	3.1×10^{-6}	8.1×10^{-9}
Corn	0.000191	10	2.8×10^{-6}	7.2×10^{-9}
Sunflower/safflower	0.000505	10	7.4×10^{-6}	1.9×10^{-8}

[a] Daily exposure = (Dermal exposure × 6.3% dermal absorption) + Inhalation Exposure
[b] LADD (Lifetime average daily dose) = (Daily exposure × Days of exposure per year × 40 years of work) / (365 days per year × 75 year life expectancy)
[c] Based on a $q_1^* = 2.59\times10^{-3}$

Table 13 Non-cancer risk assessment for treaters wearing a single layer and gloves/ planters wearing coveralls over single layer and gloves

Scenario	Dermal unit exposure (mg/kg ai handled)	Inhalation unit exposure (mg/kg ai handled)	Area planted (ha)/day	Kg seed/ha	Dermal exposure (mg/kg bw/day)[a]	Inhalation Exposure (mg/kg bw/day)[a]	Dermal MOE[b]	Inhalation MOE[c]
Treater/planter (small grower)	4.19	0.145	20	1460	0.0350	0.00121	28607	46044
Treater/planter (large grower)	4.19	0.145	80	1510	0.147	0.00500	6915	11130

[a] Exposure = [Unit exposure × Rate (0.00002 kg ai/kg seed) × Area planted/day × kg seed/ha] / 70 kg bw
[b] Based on a dermal NOAEL of 1000 mg/kg bw/day (target MOE = 100)
[c] Based on an inhalation NOAEL of 55.7 mg/kg bw/day (target MOE = 100)

Table 14 Cancer risk assessment for treaters wearing single layer and gloves/ planters wearing coveralls over single layer and gloves

Scenario	Total unit exposure (mg/kg ai handled) [a]	Daily exposure (mg/kg bw/day) [b]	Days of exposure per year[c]	LADD (mg/kg bw/day)[d]	Cancer risk[e]
Treater/planter (small grower)	0.409	0.00341	5	2.7×10^{-5}	6.9×10^{-8}
Treater/planter (large grower)	0.409	0.0141	5	1.0×10^{-4}	2.7×10^{-7}

[a] Total Unit exposure = (Dermal unit exposure × 6.3% dermal absorption) + Inhalation unit exposure
[b] Daily Exposure = (Total unit exposure × Rate × Area planted per day × kg seed/ha)/ 70 kg bw
[c] Based on 20 ha/day and a 100 ha field (small grower) and 40 ha planted/day and a 200 ha potato field (large grower)
[d] LADD (Lifetime average daily dose) = (Daily exposure × Days of exposure per year × 40 years of work) / (365 days per year × 75 year life expectancy)
[e] Based on a $q_1^* = 2.59\times10^{-3}$

Table 15 Non-cancer risk assessment for workers treating potato seed pieces in-furrow

Scenario	Unit Exposure[a] (µg/kg ai handled)		Exposure [b] (mg/kg bw/day)		MOE[c]	
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation
Farmer	84.12	2.56	0.0206	0.00626	48607	88963
Custom	84.12	2.56	0.0692	0.00179	14447	31108

[a] Unit Exposure for MLA= unit exposure for liquid open pour mixing loading + unit exposure for groundboom, open cab application

[b] Exposure = Unit Exposure × Application rate (0.16 kg ai/ha) × area treated per day (107 ha for farmers, 360 ha for custom workers) / (70 kg bw × 1000 µg/mg)

[c] Based on a dermal NOAEL of 1000 mg/kg bw/day (target MOE = 100) and an inhalation NOAEL of 55.7 mg/kg bw/day (target MOE = 100)

Table 16 Cancer risk assessment for workers treating potato seed pieces in-furrow

Scenario	Total unit exposure (µg/kg ai handled)[a]	Daily exposure (mg/kg bw/day)[b]	Days of exposure per year[c]	LADD (mg/kg bw/day)[e]	Cancer risk[e]
Farmer	7.86	0.00192	5	1.4×10^{-5}	3.6×10^{-8}
Custom	7.86	0.00647	30	2.8×10^{-4}	7.3×10^{-7}

[a] Total Unit exposure = (Dermal unit exposure × 6.3% dermal absorption) + Inhalation unit exposure

[b] Daily Exposure = (Total unit exposure × Rate × Area planted per day × kg seed/ha)/ 70 kg bw

[c] Based on 20 ha/day and a 100 ha field (small grower) and 40 ha planted/day and a 200 ha potato field (large grower)

[d] LADD (Lifetime average daily dose) = (Daily exposure × Days of exposure per year × 40 years of work) / (365 days per year × 75 year life expectancy)

[e] Based on a $q_1^* = 2.59\times10^{-3}$

Table 17 Integrated food residue chemistry summary

Nature of the residue in wheat		Reference: 1886136, 1886129
Radiolabel Position	[Pyrazole-3-14C]-penflufen and [Phenyl-UL-13C6/ 14C]-penflufen	
Test Site	Plants were grown similar to natural temperature and light conditions in a vegetation area where the glass roof was open during the sunshine periods and was automatically closed during rainfall. Plants were irrigated as needed.	
Treatment	Seed treatment	
Rate	5.3 g a.i./100 kg seed (1×) 52 g a.i./100 kg seed (10×)	4.6 g a.i./100 kg seed (1×) 53 g a.i./100 kg seed (10×)
End-Use Product	Flowable suspension (FS 50)	
Preharvest Interval	Forage 52 days Hay 95 days Grain/Straw 109 days	

Nature of the residue in wheat				**Reference: 1886136, 1886129**	
Matrix	**PHI (days)**	**[^{14}C-pyrazole]**		**[^{14}C-phenyl]**	
		TRRs (ppm)		**TRRs (ppm)**	
		1×	**10×**	**1×**	**10×**
Forage	52	0.031	0.291	0.030	0.287
Hay	95	0.080	0.479	0.077	0.646
Grain	109	0.003	0.009	0.001	0.008
Straw	109	0.186	1.814	0.175	1.502

Metabolites Identified	**Major Metabolites** (>10% of the TRRs)		**Minor Metabolites** (<10% of the TRRs)	
Radiolabel Position	**[^{14}C-pyrazole]**	**[^{14}C-phenyl]**	**[^{14}C-pyrazole]**	**[^{14}C-phenyl]**
Forage (1×)	3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	Penflufen 3-hydroxybutyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine	3-hydroxybutyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine
Hay (1×)	3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	Penflufen Pyrazole-4-carboxamide 3-hydroxybutyl-glucoside 3-hydroxybutyl Hydroxy-mercapto-lactic acid Succinyl-cysteine	Penflufen 3-hydroxybutyl-glucoside 3-hydroxybutyl Hydroxy-mercapto-lactic acid
Straw (1×)	3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-malonyl-glucoside	Pyrazole-4-carboxamide 3-hydroxybutyl-glucoside 3-hydroxybutyl 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine	3-hydroxybutyl-glucoside 3-hydroxybutyl Hydroxy-mercapto-lactic acid Succinyl-cysteine
Grain (1× and 10×)	Residues too low to further analyze.			

Nature of the residue in wheat	**Reference: 1886136, 1886129**

Metabolic Pathways
Three metabolic pathways were observed in wheat when using the pyrazole radiolabel: (i) substitution of glutathione 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, and (iii) cleavage at the N-phenyl linkage to yield penflufen-pyrazole-4-carboxamide.

Two metabolic pathways were observed in wheat when using the phenyl radiolabel: (i) substitution of glutathione for fluorine on the pyrazole ring followed by hydrolysis of the glutathione moiety to cysteine, and (ii) hydroxylation of the third or fourth carbon on the butyl substituent, followed by conjugation with glucose and malonic acid.

Nature of the residue in soybean		**Reference: 1886135, 1886124**
Radiolabel Position	[Pyrazole-3-14C]-penflufen and [Phenyl-UL-13C6/ 14C]-penflufen	
Test Site	Plants were grown in a greenhouse. Plants were irrigated as needed.	
Treatment	Seed treatment	
Rate	5.1 g a.i./100 kg seed (1×) 50 g a.i./100 kg seed (10×)	5.2 g a.i./100 kg seed (1×) 50 g a.i./100 kg seed (10×)
End-Use Product	Flowable suspension (FS 240)	
Preharvest Interval	Forage 29 days Hay 63 days Seed 116 days	Forage 30 days Hay 64 days Seed 110 days

Matrix	**PHI (days)**	**[^{14}C-pyrazole]**		**[^{14}C-phenyl]**	
		TRRs (ppm)		**TRRs (ppm)**	
		1×	**10×**	**1×**	**10×**
Forage	29/30	0.202	0.498	0.175	0.398
Hay	63/64	0.031	0.249	0.023	0.258
Seed	110/116	0.004	0.025	0.002	0.011

Metabolites Identified	**Major Metabolites** (>10% of the TRRs)		**Minor Metabolites** (<10% of the TRRs)	
Radiolabel Position	**[^{14}C-pyrazole]**	**[^{14}C-phenyl]**	**[^{14}C-pyrazole]**	**[^{14}C-phenyl]**
Forage (1×)	Homoglutathione Cysteine	Homoglutathione Cysteine	Penflufen 3-hydroxybutyl-malonyl-glucoside Succinyl-cysteine	Penflufen 3-hydroxybutyl-malonyl-glucoside Succinyl-cysteine
Hay (1×)	Homoglutathione 3-hydroxybutyl-malonyl-glucoside	Penflufen Homoglutathione 3-hydroxybutyl-malonyl-glucoside	None	None

Nature of the residue in wheat			Reference: 1886136, 1886129	
Seed (10×)	Desmethyl-dicarboxylic acid Homoglutathione	Homoglutathione	None	None

Metabolic Pathways
Three metabolic pathways were observed in soybean when using the pyrazole radiolabel: (i) cleavage of the bond between the amide nitrogen and the phenyl ring followed by hydrolysis of the resulting amide to a carboxylic acid, oxidation of the C3-methyl substituent, and loss of the N-methyl substituent to yield penflufen-desmethyl-dicarboxylic acid, (ii) hydroxylation of the butyl moiety in the 3-position, followed by conjugation with glucose and malonic acid, and (iii) hydrolysis of the fluorine substituent on the pyrazole ring, followed by glutathione conjugation and subsequent hydrolysis of the glutathione moiety.

Two metabolic pathways were observed in soybean when using the phenyl radiolabel: (i) hydroxylation of the butyl moiety in the 3-position, followed by conjugation with glucose and malonic acid, and (ii) hydrolysis of the fluorine substituent on the pyrazole ring, followed by glutathione conjugation and subsequent hydrolysis of the glutathione moiety.

Nature of the residue in potato			Reference: 1886134, 1886128	
Radiolabel Position	[Pyrazole-3-14C]-penflufen and [Phenyl-UL-13C6/ 14C]-penflufen			
Test Site	Plants were grown similar to natural temperature and light conditions in a vegetation area where the glass roof was open during the sunshine periods and was automatically closed during rainfall. Plants were irrigated as needed.			
Treatment	Seed-piece treatment and in-furrow application			
Rate	5 g a.i./100 kg seed-piece (190 g a.i./ha) 530 g a.i./ha (in-furrow)		5 g a.i./100 kg seed-piece (166 g a.i./ha) 544 g a.i./ha (in-furrow)	
End-Use Product	Suspension concentrate (100 SC)			
Preharvest Interval	Mature tubers and leaves at 140 days			

Matrix	**PHI (days)**	**[^{14}C-pyrazole]**		**[^{14}C-phenyl]**	
		TRRs (ppm)		**TRRs (ppm)**	
		Seed treatment	**In-furrow application**	**Seed treatment**	**In-furrow application**
Tubers	140	0.079	0.127	0.015	0.110
Leaves	140	--	1.675	--	--

Metabolites Identified	**Major Metabolites** (>10% of the TRRs)		**Minor Metabolites** (<10% of the TRRs)	
Radiolabel Position	**[14C-pyrazole]**	**[14C-phenyl]**	**[14C-pyrazole]**	**[14C-phenyl]**

Nature of the residue in wheat			Reference: 1886136, 1886129	
Tubers (seed treatment)	Penflufen	Penflufen 3-hydroxybutyl	3-hydroxybutyl 3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Glutathione Cysteine	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Glutathione
Tubers (in-furrow)	Penflufen	Penflufen Glutathione	3-hydroxybutyl 3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Glutathione Cysteine	3-hydroxybutyl 3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Cysteine
Leaves (in-furrow)	3-hydroxybutyl 3-hydroxybutyl-glucoside	--	Penflufen 3-hydroxybutyl-malonyl-glucoside Glutathione Cysteine	--

Metabolic Pathways
Two metabolic pathways were observed in potato when using the pyrazole or phenyl radiolabel: (i) hydroxylation of the butyl moiety in the 3-position, followed by conjugation with glucose and malonic acid, and (ii) hydrolysis of the fluorine substituent on the pyrazole ring, followed by glutathione conjugation and subsequent hydrolysis of the glutathione moiety.

Nature of the residue in paddy rice			Reference: 1886133, 1886126
Radiolabel Position	[Pyrazole-3-14C]-penflufen and [Phenyl-UL-13C6/ 14C]-penflufen		
Test Site	Plants were grown in a greenhouse.		
Treatment	Soil treatment into the planting holes during transplanting of rice (3-4 leaf stage)		
Rate	520 g a.i./ha		500 g a.i./ha
End-Use Product	2% Granule (GR 2 formulation)		
Preharvest Interval	Kernels, husks and straw 108 days		
Matrix	**PHI (days)**	**[14C-pyrazole]**	**[14C-phenyl]**
		TRRs (ppm)	**TRRs (ppm)**
Kernels	108	0.023	0.017
Husks	108	0.418	0.294
Straw	108	13.301	12.079

Nature of the residue in wheat			**Reference: 1886136, 1886129**	
Metabolites Identified	**Major Metabolites** (>10% of the TRRs)		**Minor Metabolites** (<10% of the TRRs)	
Radiolabel Position	**[14C-pyrazole]**	**[14C-phenyl]**	**[14C-pyrazole]**	**[14C-phenyl]**
Kernels	Penflufen 3-hydroxybutyl	Penflufen 3-hydroxybutyl	Sulfonic acid	None
Husks	Penflufen 3-hydroxybutyl	Penflufen 3-hydroxybutyl	Hydroxy-sulfonic acid Sulfonic acid Succinyl-cysteine	Hydroxy-sulfonic acid Sulfonic acid Succinyl-cysteine Hydroxy-mercapto-lactic acid + hydroxy-acetyl-cysteine
Straw	None	None	Penflufen 3-hydroxubutyl Desmethyl-pyrazole-4-carboxamide Pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Hydroxy-sulfonic acid Sulfonic acid Succinyl-cysteine Succinyl-cysteine-glycine Cysteinyl-succinimide Hydroxy-mercapto-lactic acid + hydroxyl-acetyl-cysteine	Penflufen 3-hydroxybutyl Hydroxy-sulfonic acid Sulfonic acid Succinyl-cysteine Succinyl-cysteine-glycine Cysteinyl-succinimide Hydroxy-mercapto-lactic acid + hydroxyl-acetyl-cysteine

Metabolic Pathways
Three basic metabolic pathways were observed in rice when using the pyrazole radiolabel: (i) cleavage of the bond between the amide nitrogen and the phenyl ring followed by hydrolysis of the resulting amide to a carboxylic acid, oxidation of the C3-methyl substituent, and loss of the N-methyl substituent to yield penflufen-desmethyl-dicarboxylic acid, (ii) hydroxylation of the butyl moiety in the 3-position, and (iii) hydrolysis of the fluorine substituent on the pyrazole ring, followed by glutathione conjugation which in turn was followed by hydrolysis of the glutathione moiety to yield sulfonic acid or various cysteine derivatives, with or without hydroxylation of the butyl moiety.

Three basic metabolic pathways were observed in rice when using the phenyl radiolabel: (i) hydroxylation of the butyl moiety in the 3-position, and (ii) hydrolysis of the fluorine substituent on the pyrazole ring, followed by glutathione conjugation, which in turn was followed by hydrolysis of the glutathione moiety to yield sulfonic acid or various cysteine derivatives, with or without hydroxylation of the butyl moiety.

Confined accumulation in rotational crops – wheat, soybean and turnip	**Reference: 1886132, 1886125**
Radiolabel Position	[Pyrazole-3-14C]-penflufen and [Phenyl-UL-13C6/ 14C]-penflufen

Nature of the residue in wheat				**Reference: 1886136, 1886129**	
Test site		Started outdoors in a walled area open to the elements with the containers being moved to a greenhouse during the second rotation.			
Formulation used for trial		Solution prepared in water:acetonitrile (3:2, v/v)			
Application rate and timing		Soil surface was treated directly with the formulated product at a rate of 532-534 g a.i./ha and aged for 30, 156-157 and 376-377 days prior to planting of rotational crops.			
Metabolites identified		**Major Metabolites** (>10% of the TRRs)		**Minor Metabolites** (<10% of the TRRs)	
Matrix	PBI (days)	**[14C-pyrazole]**	**[14C-phenyl]**	**[14C-pyrazole]**	**[14C-phenyl]**
Wheat forage	30	Desmethyl-dicarboxylic acid 3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl- glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	Penflufen Desmethyl-pyrazole-4-carboxamide Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid 3-hydroxybutyl-glucoside Hydroxy-mercapto-lactic acid Cysteine Succinyl-cysteine	Penflufen Hydroxy-mercapto-lactic acid Cysteine Succinyl-cysteine
	157	3-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	Penflufen Bis-desmethyl-3-carbonyl serine Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid 3-hydroxybutyl-glucoside 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine 3-hydroxybutyl Succinyl-cysteine	Penflufen 3-hydroxybutyl-glucoside Hydroxy-mercapto-lactic acid Cysteine Succinyl-cysteine

Nature of the residue in wheat				Reference: 1886136, 1886129	
	377	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	Penflufen Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid Hydroxy-mercapto-lactic acid Succinyl-cysteine	Penflufen Hydroxy-mercapto-lactic acid Succinyl-cysteine
Wheat hay	30	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	Penflufen Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine	Penflufen 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine
	157	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Pyrazole-4-carboxamide	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside	Penflufen Bis-desmethyl-3-carbonyl serine Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine	Penflufen Hydroxy-mercapto-lactic acid Succinyl-cysteine
	377	3-hydroxybutyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-	Penflufen Bis-desmethyl-3-	Penflufen Hydroxy-mercapto-

Nature of the residue in wheat				Reference: 1886136, 1886129	
		3-hydroxybutyl-malonyl-glucoside	glucoside 4-hydroxybutyl-malonyl-glucoside	carbonyl serine Desmethyl-pyrazole-4-carboxamide Pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine 3-hydroxybutyl Succinyl-cysteine	lactic acid 3-hydroxybutyl Succinyl-cysteine
Wheat straw	30	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	Penflufen Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine	Penflufen 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine 3-hydroxybutyl Succinyl-cysteine
	157	Pyrazole-4-carboxamide 3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine	Penflufen 4-hydroxybutyl-malonyl-glucoside Cysteine 3-hydroxybutyl Hydroxy-mercapto-lactic acid Succinyl-cysteine

Nature of the residue in wheat				Reference: 1886136, 1886129	
	377	3-hydroxybutyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl	Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid 3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid 3-hydroxybutyl	3-hydroxybutyl-malonyl-glucoside 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine Succinyl-cysteine
Wheat grain	30	Bis-desmethyl-3-carbonyl serine Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid	4-hydroxybutyl-malonyl-glucoside	None	None
	157	Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid	None	Desmethyl-dicarboxylic acid	None
	377	Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid	None	None	None
Soybean forage	30	Desmethyl-dicarboxylic acid 3-hydroxybutyl-malonyl-glucoside Homoglutathione	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Penflufen Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid	Penflufen Hydroxy-mercapto-lactic acid Cysteine Succinyl-cysteine

Nature of the residue in wheat				Reference: 1886136, 1886129	
	157	Bis-desmethyl-3-carbonyl serine Desmethyl-dicarboxylic acid 3-hydroxybutyl-malonyl-glucoside Homoglutathione	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Penflufen Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide 3-hydroxybutyl-glucoside Cysteine Succinyl cysteine	Penflufen 3-hydroxybutyl-glucoside 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine Succinyl-cysteine
	377	3-hydroxybutyl-malonyl-glucoside Homoglutathione	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Penflufen Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Hydroxyl-mercapto-lactic acid Cysteine	Penflufen 3-hydroxybutyl-glucoside 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine
Soybean hay	30	Desmethyl-dicarboxylic acid Homoglutathione	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Pyrazole-4-carboxamide Bis-desmethyl-3-carboxylic acid 3-hydroxybutyl-malonyl-glucoside	Penflufen 3-hydroxybutyl-glucoside Hydroxy-mercapto-lactic acid Cysteine Succinyl-cysteine
	157	Bis-desmethyl-3-carbonyl serine Bis-desmethyl-3-carboxylic acid 3-hydroxybutyl-malonyl-glucoside Desmethyl-dicarboxylic acid Homoglutathione	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Pyrazole-4-carboxamide	Penflufen 3-hydroxybutyl-glucoside 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine 3-hydroxybutyl Succinyl-cysteine

Nature of the residue in wheat				Reference: 1886136, 1886129	
	377	3-hydroxybutyl-malonyl-glucoside Homoglutathione	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Penflufen Bis-desmethyl-3-carbonyl serine Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid 3-hydroxybutyl-glucoside	Penflufen 3-hydroxybutyl-glucoside 4-hydroxybutyl-malonyl-glucoside Cysteine Succinyl-cysteine
Soybean seed	30	Bis-desmethyl-3-carbonyl serine Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Pyrazole-4-carboxamide	3-hydroxybutyl-glucoside Hydroxy-mercapto-lactic acid Cysteine 3-hydroxybutyl
	157	Bis-desmethyl-3-carbonyl serine Bis-desmethyl-3-carboxylic acid	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Desmethyl-dicarboxylic acid Pyrazole-4-carboxamide	None
	377	Bis-desmethyl-3-carbonyl serine Bis-desmethyl-3-carboxylic acid	3-hydroxybutyl-malonyl-glucoside Homoglutathione	Desmethyl-dicarboxylic acid	Cysteine
Turnip leaves	30	Desmethyl-pyrazole-4-carboxamide Pyrazole-4-carboxamide 3-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	Bis-desmethyl-3-carbonyl serine Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid 3-hydroxybutyl-glucoside 4-hydroxybutyl-malonyl-glucoside Glutathione	Penflufen 4-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Succinyl-cysteine Cysteine 3-hydroxybutyl Glutathione

Nature of the residue in wheat				Reference: 1886136, 1886129	
	157	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside	Bis-desmethyl-3-carbonyl serine Desmethyl-pyrazole-4-carboxamide Pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Glutathione Succinyl cysteine	Penflufen 4-hydroxybutyl-malonyl-glucoside Glutathione
	377	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Desmethyl-pyrazole-4-carboxamide	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Glutathione	Penflufen Pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid 4-hydroxybutyl-malonyl-glucoside Glutathione 3-hydroxybutyl Succinyl cysteine	Penflufen 4-hydroxybutyl-malonyl-glucoside Cysteine 3-hydroxybutyl Succinyl-cysteine
Turnip roots	30	Pyrazole-4-carboxamide Glutathione	Penflufen Glutathione	Penflufen Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid Fluoro acid 3-hydroxybutyl-glucoside Cysteine 3-hydroxybutyl Succinyl cysteine	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Hydroxy-mercapto-lactic acid Cysteine 3-hydroxybutyl Succinyl-cysteine

Nature of the residue in wheat				Reference: 1886136, 1886129	
	157	Pyrazole-4-carboxamide Glutathione	Penflufen Glutathione	Penflufen Desmethyl-pyrazole-4-carboxamide Desmethyl-dicarboxylic acid Bis-desmethyl-3-carboxylic acid Fluoro acid 3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside 3-hydroxybutyl Succinyl cysteine	3-hydroxybutyl-glucoside 3-hydroxybutyl Succinyl-cysteine
	377	Glutathione	Penflufen Glutathione	Penflufen Pyrazole-4-carboxamide Fluoro acid 3-hydroxybutyl-glucoside Cysteine 3-hydroxybutyl Succinyl cysteine	3-hydroxybutyl-glucoside 3-hydroxybutyl-malonyl-glucoside Cysteine 3-hydroxybutyl Succinyl-cysteine

Metabolic Pathways

Four basic metabolic pathways were observed in rotational crops when using the pyrazole radiolabel: (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.

Two basic metabolic pathways were observed in rotational crops when using the phenyl radiolabel: (i) substitution of glutathione or homoglutathione for fluorine on the pyrazole ring followed by hydrolysis of the glutathione moiety to cysteine, and (ii) hydroxylation of the third or fourth carbon on the butyl substituent, followed by conjugation with glucose and malonic acid.

TRR study in rotational crops – wheat, Swiss chard and turnip	Reference: 1886072

A study was carried out with [phenyl-UL-$^{13}C_6/^{14}C$] and [pyrazole-3-^{14}C]penflufen, each applied by spray treatment to the bare soil (sandy loam) of a 1.0 m^2 planting container at an application rate of 10 g a.i./ha. Three rotational crops, spring wheat, Swiss chard and turnips were each sown at 30, 139 and 287 days after application, representing the first, second and third rotation. The application, 30 day ageing period and the cultivation of crops of the first rotation and part of the second rotation was conducted in a walled area open to the elements, the remainder of the study was conducted in a greenhouse. 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.

Nature of the residue in wheat	Reference: 1886136, 1886129

TRRs observed in harvested samples were low. The highest TRRs were in wheat straw of the first rotation (~0.06 ppm for both labels). Apart from wheat straw, only wheat hay and forage (2nd rotation) had TRRs above 0.01 ppm. Samples of Swiss chard and turnips from the second and third rotation were not radioassayed due to the low TRRs (<0.01 ppm) in these commodities from the first rotation. For wheat straw (phenyl label) the TRRs decreased from 0.59 ppm in the first rotation to 0.18 ppm in the second and remained at a similar level (0.019 ppm) for the third rotation. For the pyrazole label, the TRRs in straw decreased from 0.058 ppm in the first rotation to 0.04 ppm in the second and 0.022 ppm in the third. TRRs in hay of the first rotation were lower than those in straw, at 0.022 and 0.027 ppm for the phenyl and pyrazole labels, respectively. However, there was less decline in the second and third rotations compared to straw. For the second rotation, the TRRs in hay were 0.014 ppm for both labels, increasing slightly to 0.016 and 0.20 ppm in the third rotation for the phenyl and pyrazole labels, respectively. TRRs in wheat forage and wheat grain were at similar levels for all three rotations. The TRRs in forage ranged from 0.007 to 0.011 ppm for both labels, while those in grain ranged from 0.001 to 0.004 ppm.

Samples with TRRs above 0.01 ppm (wheat hay and straw, and forage of the 2nd rotation) were extracted with acetonitrile/water mixtures prior to analysis of metabolites. Approximately 77-91% of the TRRs were extractable. Radioactivity remaining in the solids after extraction ranged from about 9 to 23% of the TRRs and was always ≤0.010 ppm (for most of the samples ≤0.004 ppm).

Seven metabolites were identified, two of which were specific to the pyrazole label. No metabolites specific to the phenyl label were identified. Penflufen accounted for ≤12% of the TRRs in all wheat samples from the 1st and 2nd rotations and was not detected in the 3rd rotation. Metabolites detected were: 3-hydroxybutyl-glucoside at up to 14% of the TRRs in the 1st and 2nd rotations and not detected in the 3rd. 3-hydroxybutyl-malonyl-glucoside was found in all three rotations up to a maximum of 49% of the TRRs in wheat hay of the third rotation (phenyl label). 4-hydroxybutyl-malonyl-glucoside was found at up to 27% of the TRRs in the 1st and 2nd rotations and not detected in the 3rd. Hydroxy-mercapto-lactic acid was detected in all rotations, except the 3rd rotation for the pyrazole label, at up to 18.9% of the TRRs. Succinyl-cysteine was detected in all rotations, except the 2nd for the phenyl label and the 3rd for the pyrazole label. The highest TRRs for succinyl-cysteine was 15.9% in hay of the 3rd rotation (phenyl label). Desmethyl-pyrazole-4-carboxamide, which is specific to the pyrazole label, increased with each rotation from up to 4.4% of the TRRs in the 1st rotation to up to 42.9% of the TRRs in the 3rd. Desmethyl-dicarboxylic acid, also specific to the pyrazole label, also increased with each rotation from up to 4.0% of the TRRs in the 1st rotation to up to 34.7% of the TRRs in the 3rd. None of the identified metabolites accounted for more than 0.009 ppm in any sample. In all, 40-83% of the TRRs were identified. Eleven unknown metabolites were characterized, none accounting for more than 0.009 ppm in any sample.

Metabolic Pathways

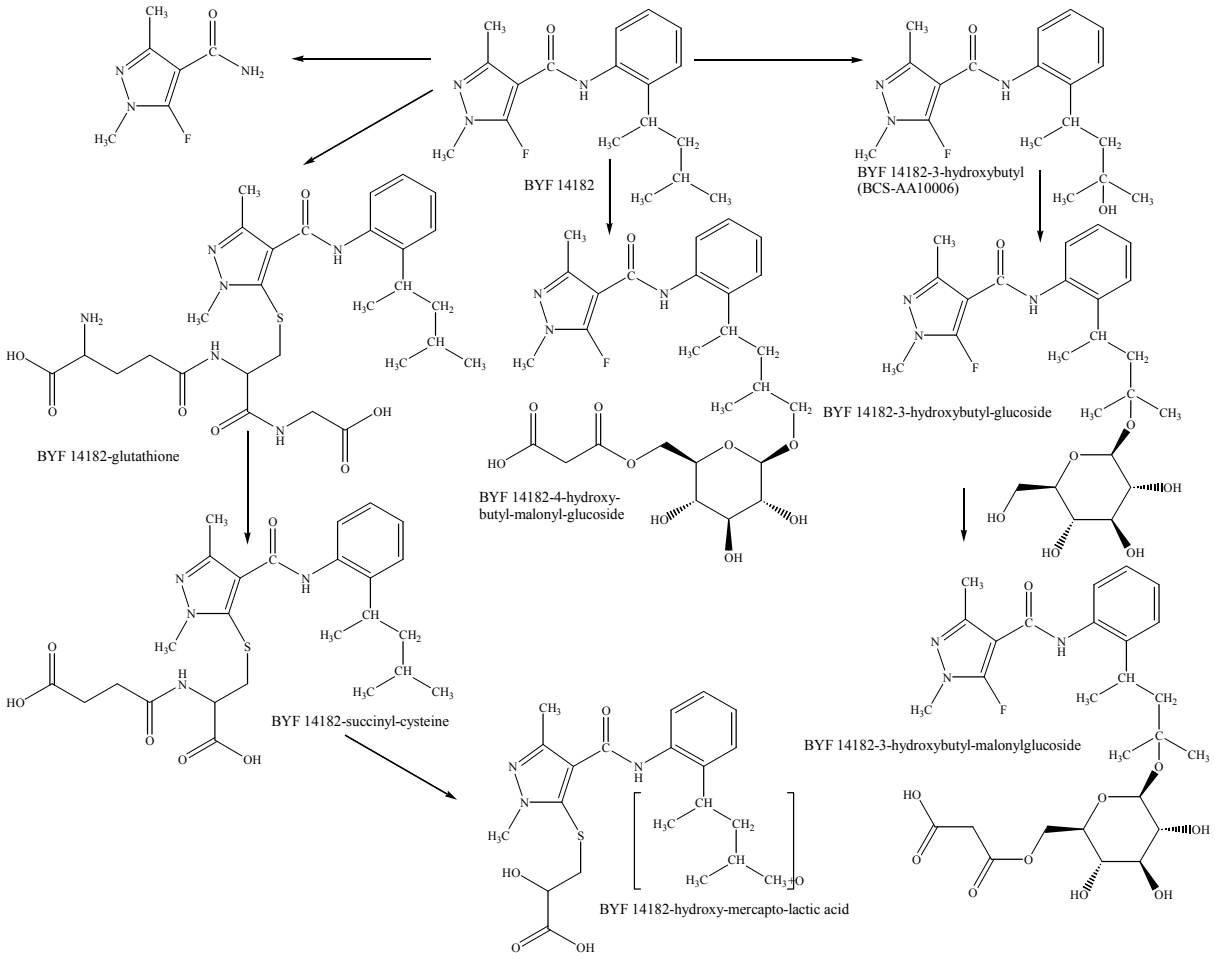
Four metabolic pathways for penflufen were observed **in rotational crops in TRR studies**: (i) hydroxylation at the 3- or 4- position of the alkyl side chain followed by conjugation with glucose and malonic acid; (ii) conjugation with glutathione via substitution of the fluorine atom followed by metabolic 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; and (iv) cleavage of the *N*-phenyl bond followed by *N*-demethylation to release the pyrazole-4-carboxamide.

Overview of metabolism in plants

The metabolism of penflufen in plants is adequately documented. Metabolic pathways and major metabolites observed were similar in primary crops (wheat, soybean, potato and paddy rice) and in rotational crops (wheat, soybean, turnip, Swiss chard). The residue definition in plants is penflufen for enforcement and risk assessment purposes.

Proposed metabolic scheme in wheat (representative of metabolism in primary crops):

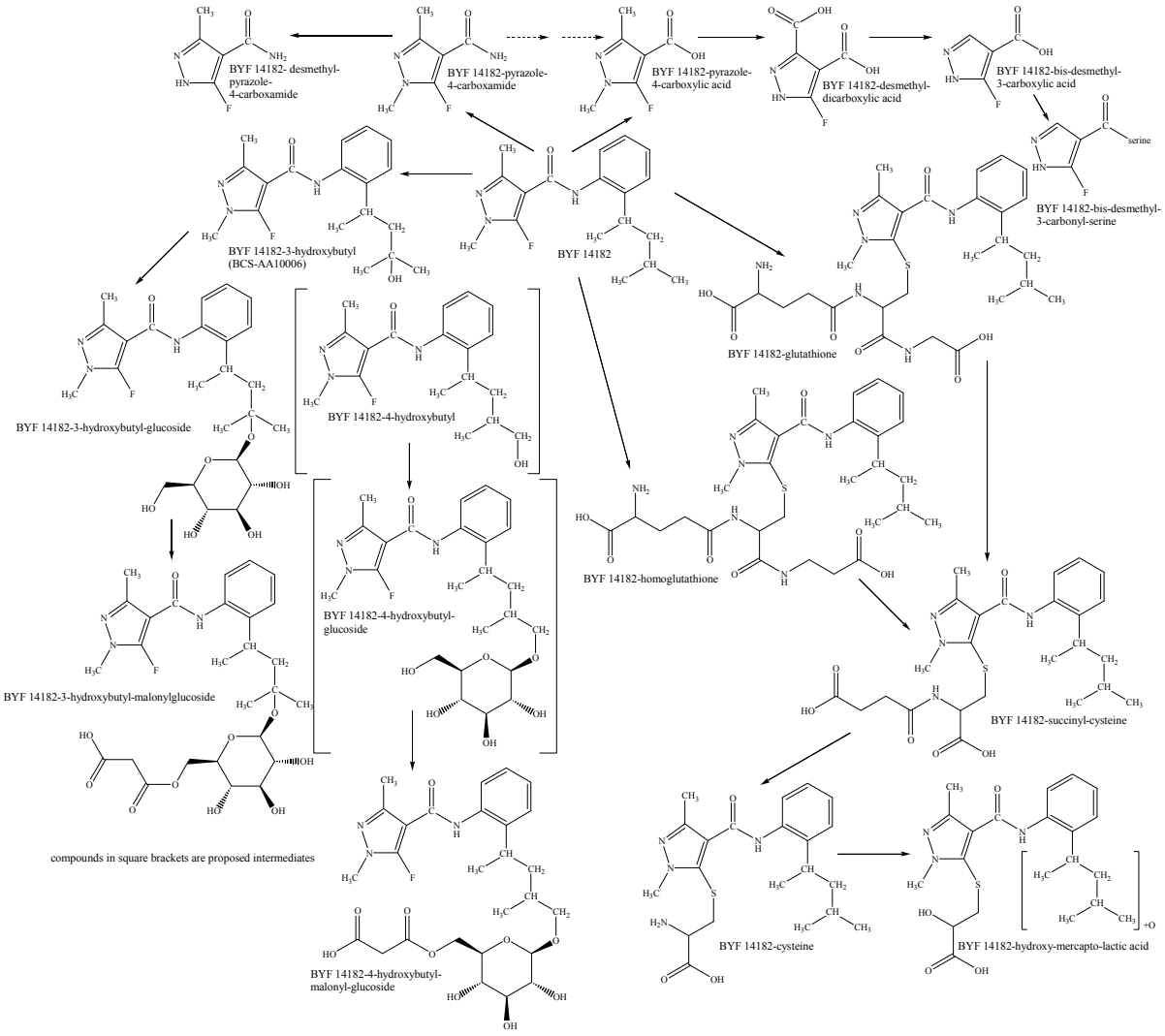
Nature of the residue in wheat	Reference: 1886136, 1886129



Proposed metabolic pathways in wheat following seed treatment with [pyrazole-3-^{14}C]penflufen.

Nature of the residue in wheat	Reference: 1886136, 1886129

Proposed metabolic scheme in rotational crops



Proposed metabolic pathways in rotational crops when soil is treated with [pyrazole-3-^{14}C]penflufen.

Nature of the residue in laying hen	Reference: 1886131, 1886123

Phenyl radiolabel:
Six laying hens were administered a single daily oral dose for 14 consecutive days at an average dose of 27.38 mg/kg of feed of [Phenyl-UL-$^{13}C_6$/ ^{14}C]-penflufen. The hens were sacrificed ~6 hours after the last dose.

Greater than 94% of the administered dose (AD) was eliminated in the excreta. The radioactivity present in eggs was 0.139% of AD while 0.206% of AD was present in organs and tissues. The highest concentration of radioactivity in tissues was observed in liver (0.619 ppm) and kidney (0.401 ppm). The TRRs in eggs ranged from 0.052 ppm to 0.143 ppm and reached a plateau at day 8.

Nature of the residue in wheat	Reference: 1886136, 1886129

Pyrazole radiolabel:
Six laying hens were administered a single daily oral dose for 14 consecutive days at an average dose of 25.24 mg/kg of feed of [Pyrazole-3-^{14}C]-penflufen. The hens were sacrificed ~6 hours after the last dose.

Greater than 94% of the administered dose (AD) was eliminated in the excreta. The radioactivity present in eggs was 0.112% of AD while 0.214% of AD was present in organs and tissues. The highest concentration of radioactivity in tissues was observed in liver (0.636 ppm) and kidney (0.378 ppm). The TRRs in eggs ranged from 0.002 ppm to 0.098 ppm and reached a plateau at day 6.

Metabolic Pathways
The main metabolic pathways in the laying hen dosed with the ***phenyl radiolabel*** were:
i) *N*-demethylation in the pyrazole ring,
ii) hydroxylation at the following positions of the molecule: the alkyl side chain of the phenyl ring, the 4'-position of the phenyl ring and the methyl group in the position 3 of the pyrazole ring,
iii) further oxidation of the hydroxy group in the 2-position of the alkyl side chain forming a keto group,
iv) oxidative cleavage of the alkyl side chain forming an acetyl compound,
v) conjugation of the hydroxy group in the 4'-position of the phenyl ring with glucuronic acid, and
vi) further oxidation of the hydroxymethyl group of the pyrazole ring forming a carboxylic acid group.

The main metabolic pathways in the laying hen dosed with the ***pyrazole radiolabel*** were:
i) *N*-demethylation in the pyrazole ring,
ii) hydroxylation at the following positions of the molecule: the alkyl side chain of the phenyl ring, the 4'-position of the phenyl ring and the methyl group in position 3 of the pyrazole ring,
iii) further oxidation of the hydroxy group in the 2-position of the alkyl side chain forming a keto group,
iv) oxidative cleavage of the alkyl side chain forming an acetyl compound,
v) conjugation of the hydroxy group in the 4'-position of the phenyl ring with glucuronic acid,
vi) further oxidation of the hydroxymethyl group of the pyrazole ring forming a carboxylic acid group,
vii) cleavage of the carboxamide bond forming a carboxylic acid group, which was further metabolised via conjugation with glucuonic acid and
viii) cleavage of the N-phenyl bond forming a carboxamide.

Matrices	[Phenyl-UL-$^{13}C_6$/^{14}C]-penflufen		[Pyrazole-3-^{14}C]-penflufen	
	TRRs (ppm)	% of AD	TRRs (ppm)	% of AD
Excreta (day 1-14)	Not reported	94.2	Not reported	94.7
Leg muscle	0.051	0.019	0.056	0.02
Breast muscle	0.040	0.013	0.038	0.02
Liver	0.619	0.058	0.636	0.06
Kidney	0.401	0.010	0.378	0.01
Eggs from ovary/oviduct	0.194	0.015	0.160	0.02
Eggs (day 1-14)	0.102	0.139	0.069	0.11
Body skin	0.108	0.015	0.138	0.02
Body fat	0.098	0.046	0.103	0.046
Total	**--**	**94.6**	**--**	**95.1**

Nature of the residue in wheat			**Reference: 1886136, 1886129**	
Metabolites identified	**Major metabolites** (>10% of the TRRs)		**Minor metabolites** (<10% of the TRRs)	
Radiolabel Position	**[^{14}C-phenyl]**	**[^{14}C-pyrazole]**	**[^{14}C-phenyl]**	**[^{14}C-pyrazole]**
Eggs	Penflufen (0.012 ppm)	None	3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4'-trihydroxy 1,3,4'-trihydroxy Desmethyl-hydroxymethyl-2,3-dihydroxy Desmethyl-dihydroxy 3,4'-dihydroxy-ketone Dihydroxy (isomer 1) Dihydroxy (isomer 2) 3,4'-dihydroxy Hydroxy-keto-carboxylic acid 4'-hydroxy-glucuronide (isomer 1) 4'-hydroxy-glucuronide (isomer 2) Desmethyl-3-hydroxy-ketone Desmethyl-acetyl-carboxylic acid 3-hydroxybutyl	Penflufen Desmethyl-pyrazole-4-carboxamide and desmethyl-4-carboxylic acid-glucuronide Desmethyl-4-carboxylic acid Fluoro acid 3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4'-trihydroxy 1,3,4'-trihydroxy Desmethyl-hydroxymethyl-2,3-dihydroxy Desmethyl-dihydroxy 3,4'-dihydroxy-ketone Dihydroxy (isomer 1) Dihydroxy (isomer 2) 3,4'-dihydroxy Hydroxy-keto-carboxylic acid 4'-hydroxy-glucuronide (isomer 1) 4'-hydroxy-glucuronide (isomer 2) Desmethyl-3-hydroxy-ketone Desmethyl-acetyl-carboxylic acid 3-hydroxybutyl

Nature of the residue in wheat				Reference: 1886136, 1886129
Muscle	3,4'-dihydroxy-keto-glucuronide (0.005 ppm)	None	3,4'-dihydroxy-glucuronide 2,3,4'-trihydroxy 1,3,4'-trihydroxy Desmethyl-hydroxymethyl-2,3-dihydroxy Desmethyl-dihydroxy 3,4'-dihydroxy-ketone Dihydroxy (isomer 1) Dihydroxy (isomer 2) 3,4'-dihydroxy Hydroxy-keto-carboxylic acid	Desmethyl-pyrazole-4-carboxamide and desmethyl-4-carboxylic acid-glucuronide Desmethyl-4-carboxylic acid 3,4'-dihydroxy-glucuronide 2,3,4'-trihydroxy 1,3,4'-trihydroxy Desmethyl-hydroxymethyl-2,3-dihydroxy Desmethyl-dihydroxy 3,4'-dihydroxy-ketone Dihydroxy (isomer 1) Dihydroxy (isomer 2) 3,4'-dihydroxy Hydroxy-keto-carboxylic acid
Fat	Penflufen (0.077 ppm)	Penflufen (0.077 ppm)	3-hydroxybutyl	3-hydroxybutyl
Liver	None	None	3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4'-trihydroxy 1,3,4'-trihydroxy Desmethyl-hydroxymethyl-2,3-dihydroxy Desmethyl-dihydroxy 3,4'-dihydroxy-ketone Dihydroxy (isomer 2) 3,4'-dihydroxy Hydroxy-keto-carboxylic acid 4'-hydroxy-glucuronide (isomer 2) Desmethyl-3-hydroxy-ketone	Desmethyl-pyrazole-4-carboxamide and desmethyl-4-carboxylic acid-glucuronide Desmethyl-4-carboxylic acid Fluoro acid 3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4'-trihydroxy 1,3,4'-trihydroxy Desmethyl-hydroxymethyl-2,3-dihydroxy Desmethyl-dihydroxy 3,4'-dihydroxy-ketone 3,4'-dihydroxy Hydroxy-keto-carboxylic acid 4'-hydroxy-glucuronide (isomer 2) Desmethyl-3-hydroxy-ketone
Nature of the residue in lactating goat				**Reference: 1886130, 1886137**

Nature of the residue in wheat	Reference: 1886136, 1886129

Phenyl radiolabel:
One lactating goat was administered a single daily dose for 5 consecutive days at levels of 47.64 mg/kg feed of [Phenyl-UL-$^{13}C_6$/ ^{14}C]-penflufen. The goat was sacrificed ~24 hours after the last dose.

Greater than 76% of the AD was eliminated in the excreta (~60% in feces and ~16% in urine). Milk contained 0.203% of the AD. The TRRs in milk ranged from 0.028 ppm to 0.097 ppm. A plateau was reached at about 32 hours after the first dosing. The highest concentration of radioactivity in tissues was observed in liver (0.297 ppm) corresponding to 0.067% of the AD.

Pyrazole radiolabel:
One lactating goat was administered a single daily dose for 5 consecutive days at levels of 48.28 mg/kg feed of [Pyrazole-3-^{14}C]-penflufen. The goat was sacrificed ~24 hours after the last dose.

Greater than 83% of the AD was eliminated in the excreta (~72% in feces and ~11% in urine). Milk contained 0.104% of the AD. The TRRs in milk ranged from 0.028 ppm to 0.084 ppm. A plateau was reached at about 72 hours after the first dosing. The highest concentration of radioactivity in tissues was observed in liver (0.319 ppm) corresponding to 0.062% of the AD.

Metabolic Pathways
The main metabolic pathways in the laying hen dosed with the ***phenyl radiolabel*** were:
i) *N*-demethylation in the pyrazole ring,
ii) hydroxylation at the following positions of the molecule: the alkyl side chain of the phenyl ring and the 4'-position of the phenyl ring,
iii) further oxidation of the hydroxy group in the 2-position of the alkyl side chain forming a keto group,
iv) oxidation of a terminal methyl group of the alkyl side chain to a carboxylic acid group,
v) conjugation of the hydroxy group in the 4'-position of the phenyl ring with glucuronic acid, and

The main metabolic pathways in the laying hen dosed with the ***pyrazole radiolabel*** were:
i) *N*-demethylation in the pyrazole ring,
ii) hydroxylation at the following positions of the molecule: the alkyl side chain of the phenyl ring and the 4'-position of the phenyl ring,
iii) further oxidation of the hydroxy group in the 2-position of the alkyl side chain forming a keto group,
iv) oxidation of a terminal methyl group of the alkyl side chain to a carboxylic acid group,
v) conjugation of the hydroxy group in the 4'-position of the phenyl ring with glucuronic acid,
vi) cleavage of the *N*-phenyl and carboxamide bond.

Matrices	[Phenyl-UL-$^{13}C_6$/ ^{14}C]-penflufen		[Pyrazole-3-^{14}C]-penflufen	
	TRRs (ppm)	% of AD	TRRs (ppm)	% of AD
Liver	0.297	0.067	0.319	0.062
Kidney	0.126	0.005	0.084	0.003
Muscle	0.012	0.036	0.009	0.027
Fat	0.018	0.021	0.013	0.016
Milk (0-120h)	0.053 (mean)	0.203	0.046 (mean)	0.104
Urine (0-120h)	--	16.392	--	11.274
Faeces (0-120h)	--	59.943	--	71.978
Total	**--**	**76.666**	**--**	**84.463**

Nature of the residue in wheat			**Reference: 1886136, 1886129**	
Metabolites identified	**Major metabolites** (>10% of the TRRs)		**Minor metabolites** (<10% of the TRRs)	
Radiolabel position	**[^{14}C-phenyl]**	**[^{14}C-pyrazole]**	**[^{14}C-phenyl]**	**[^{14}C-pyrazole]**
Liver	3,4'-dihydroxy-glucuronide (0.044 ppm)	3,4'-dihydroxy-glucuronide (0.033 ppm)	Penflufen 3,4'-dihydroxy-keto-glucuronide 2,3,4'-trihydroxy (isomers 1 and 2) 2,3,4-trihydroxy 3,4,4'-trihydroxy Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone 3,4'-dihydroxy Pentanoic acid (isomers 1 and 2)	Fluoro acid 3,4'-dihydroxy-keto-glucuronide 2,3,4'-trihydroxy (isomers 1 and 2) 3,4,4'-trihydroxy Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone 3,4'-dihydroxy Pentanoic acid (isomers 1 and 2)
Kidney	3,4'-dihydroxy-glucuronide (0.017 ppm) Pentanoic acid (isomer 2) (0.020 ppm)	3,4'-dihydroxy-glucuronide (0.009 ppm) Pentanoic acid (isomer 2) (0.015 ppm)	3,4'-dihydroxy-keto-glucuronide 2,3,4'-trihydroxy (isomer 1) 2,3,4-trihydroxy 3,4,4'-trihydroxy Desmethyl-2,3-dihydroxy Desmethyl-dihydroxy-ketone Desmethyl-pentanoic acid 3,4'-dihydroxy-ketone 3,4'-dihydroxy Pentanoic acid (isomer 1)	Fluoro acid 3,4'-dihydroxy-keto-glucuronide 2,3,4'-trihydroxy (isomer 1) 2,3,4-trihydroxy 3,4,4'-trihydroxy Desmethyl-2,3-dihydroxy Desmethyl-dihydroxy-ketone Desmethyl-pentanoic acid 3,4'-dihydroxy-ketone 3,4'-dihydroxy Pentanoic acid (isomer 1)
Fat	3,4'-dihydroxy-glucuronide (0.002 ppm) Penflufen (0.003 ppm)	3,4'-dihydroxy-glucuronide (0.002 ppm) Penflufen (0.006 ppm) 3,4'-dihydroxy (0.002 ppm)	3,4'-dihydroxy-glucuronide Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone 3,4'-dihydroxy Desmethyl-pentanoic acid Pentanoic acid (isomers 1 and 2)	Pentanoic acid (isomer 1)

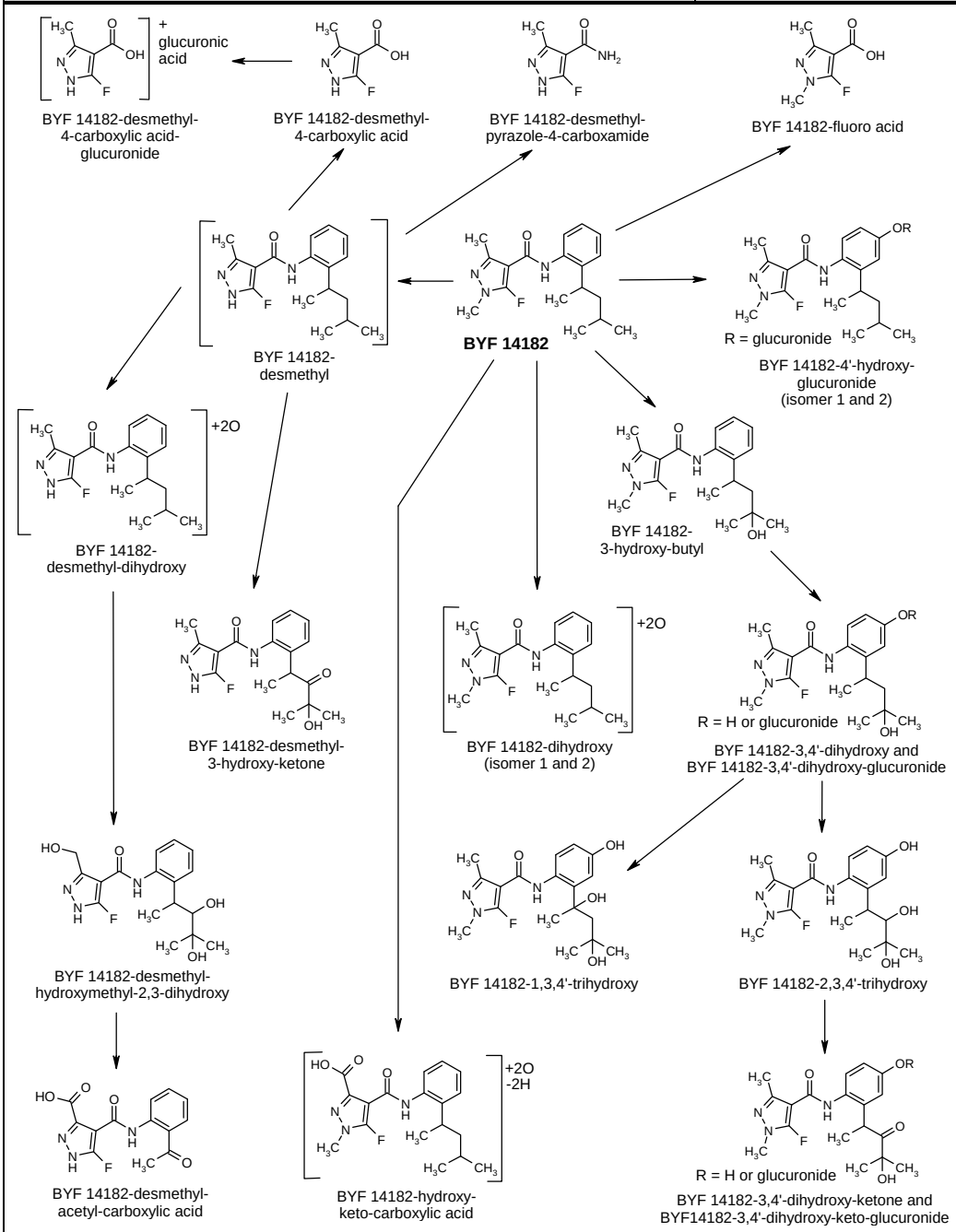
Nature of the residue in wheat				Reference: 1886136, 1886129
Muscle	3,4'-dihydroxy (0.002 ppm)	3,4'-dihydroxy (0.002 ppm)	3,4'-dihydroxy-glucuronide 3,4'-dihydroxy-keto-glucuronide 2,3,4'-trihydroxy (isomers 1 and 2) 2,3,4-trihydroxy 3,4,4'-trihydroxy Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone Pentanoic acid (isomers 1 and 2)	Penflufen 3,4'-dihydroxy-glucuronide 3,4'-dihydroxy-keto-glucuronide 2,3,4'-trihydroxy (isomer 1) 2,3,4-trihydroxy 3,4,4'-trihydroxy Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone Pentanoic acid (isomer 2)
Morning Milk	2,3,4'-trihydroxy (isomer 1) (0.008 ppm) 2,3,4'-trihydroxy (isomer 2) (0.003 ppm) 3,4'-dihydroxy (0.004 ppm)	2,3,4'-trihydroxy (isomer 1) (0.008 ppm)	3,4,4'-trihydroxy 3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4-trihydroxy Desmethyl-dihydroxy-ketone Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone	3,4,4'-trihydroxy 2,3,4'-trihydroxy (isomer 2) 3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4-trihydroxy Desmethyl-dihydroxy-ketone Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone 3,4'-dihydroxy
Evening Milk	2,3,4'-trihydroxy (isomer 1) (0.016 ppm) 3,4'-dihydroxy (0.014 ppm)	2,3,4'-trihydroxy (isomer 1) (0.011 ppm) 3,4'-dihydroxy (0.009 ppm)	2,3,4'-trihydroxy (isomer 2) 3,4,4'-trihydroxy 3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4-trihydroxy Desmethyl-dihydroxy-ketone Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone	Penflufen 3,4,4'-trihydroxy 2,3,4'-trihydroxy (isomer 2) 3,4'-dihydroxy-keto-glucuronide 3,4'-dihydroxy-glucuronide 2,3,4-trihydroxy Desmethyl-dihydroxy-ketone Desmethyl-2,3-dihydroxy 3,4'-dihydroxy-ketone Desmethyl-pentanoic acid

Overview of metabolism in animals

The metabolism of penflufen in animals is adequately documented. Metabolic pathways and major metabolites observed were similar in ruminants, poultry and rats. The residue definition in animals is penflufen for enforcement and risk assessment purposes.

Proposed metabolic scheme in poultry (representative of metabolism in livestock):

Nature of the residue in wheat	Reference: 1886136, 1886129



Proposed metabolic pathways in laying hens when dosed with [pyrazole-3-^{14}C]penflufen.

Sorage stability	Reference: 1886180, 2068943

Penflufen residues were shown to be stable at -18°C for up to 26 months in/on potato, lettuce, dry bean seed, orange, wheat grain, wheat straw and sunflower seed.

Crop field trials – beans and peas	Reference: 1886002

Twenty residue trials were conducted in Canada and the United States during the 2008 growing season (five trials on succulent peas, seven trials on dry peas, three trials on succulent beans and five trials on dry beans) to measure the magnitude of penflufen residues following the planting of seeds treated with penflufen at a rate of 5 g a.i./100 kg

Nature of the residue in wheat	Reference: 1886136, 1886129
seed. Following treatment, the seeds were planted at seeding rates corresponding to soil application rates of 2 to 14 g penflufen/ha. Residues of penflufen were less than the LOQ (<0.01 ppm) in/on succulent beans (at PHIs of 49-83 days), succulent peas (at PHIs of 52-78 days), dry bean seeds (at PHIs of 69-118 days), dry pea seeds (at PHIs of 89-113 days), dry bean forage (at PHIs of 33-60 days), dry bean hay (at PHIs of 69-100 days), dry pea vines and dry pea hay (both at PHIs of 52-77 days).	
Crop field trials – soybeans	**Reference: 1885938**
Field trials were conducted at seven locations in Canada and the United States during the 2008 growing season to measure the magnitude of penflufen residues following the planting of seeds treated with penflufen at a rate of 5 g a.i./100 kg seed. Following treatment, the seeds were planted at seeding rates corresponding to soil application rates of 2 to 7 g penflufen/ha. Residues of penflufen were less than the LOQ (<0.01 ppm) in/on soybean seed (at PHIs of 110-163 days), forage (at PHIs of 34-58 days) and hay (at PHIs of 60-83 days).	
Crop field trials – wheat	**Reference: 1886004**
Field trials were conducted at nine locations in Canada and the United States during the 2008 growing season to measure the magnitude of penflufen residues following the planting of seeds treated with penflufen at a rate of 5 g a.i./100 kg seed. Following treatment, the seeds were planted at seeding rates corresponding to soil application rates of 5 to 7 g penflufen/ha. Residues of penflufen were less than the LOQ (<0.01 ppm) in/on wheat grain and straw (both at PHIs of 96-286 days), wheat forage (at PHIs of 35-210 days) and wheat hay (at PHIs of 61-244 days).	
Crop field trials – barley	**Reference: 1886037**
Field trials were conducted at twelve locations across Canada during the 2008 growing season to measure the magnitude of penflufen residues following the planting of seeds treated with penflufen at a rate of 5.33 g a.i./100 kg seed. Following treatment, the seeds were planted at seeding rates corresponding to soil application rates of 4.6 to 6.2 g penflufen/ha. Residues of penflufen were less than the LOQ (<0.01 ppm) in/on barley grain and straw (both at PHIs of 98-112 days) and barley hay (at PHIs of 51-87 days).	
Crop field trials – corn	**Reference: 1885997**
Field trials were conducted at nine locations in Canada and the United States during the 2008 growing season to measure the magnitude of penflufen residues following the planting of seeds treated with penflufen at a rate of 10 g a.i./100 kg seed [exaggerated rate]. Following treatment, the seeds were planted at seeding rates rcorresponding to soil application rates of 2 to 3 g penflufen/ha. Residues of penflufen were less than the LOQ (<0.01 ppm) in/on sweet corn K+CWHR and forage (both at PHIs of 75-112 days), field corn forage (at PHIs of 93-139 days), field corn grain and stover (both at PHIs of 140-191 days).	
TRR studies – sunflower	**Reference: 1886071**
Sunflower seeds, treated with [pyrazole-3-^{14}C]penflufen at a rate of 18.56 g a.i./100 kg seed, were planted, grown to maturity and the seeds from mature sunflowers were harvested 115 days after planting. The progeny sunflower seeds were homogenized and radio-assayed. The lower limit of method validation (LLMV) was 0.05 ppm. The method limit of detection (LOD) was calculated to be 0.0016 ppm in sunflower seeds. The TRRs in mature sunflower seeds were <0.0016 ppm (<LOD) in all samples.	

Nature of the residue in wheat	**Reference: 1886136, 1886129**
TRR studies – canola	**Reference: 1886067**
Canola seeds, treated with [pyrazole-3-^{14}C]penflufen at a rate of 15.65 g a.i./100 kg seed, were planted, and the canola was grown to maturity. The canola was harvested at maturity 84 days after planting, the seeds were collected, homogenized and radio-assayed. The LLMV was 0.05 ppm. The LOD in canola seed was calculated to be 0.00064 ppm. The TRRs in the mature canola seeds were <0.00064 ppm (<LOD) in all samples.	
TRR studies – cotton	**Reference: 1886069**
Cotton seeds, treated with [pyrazole-3-^{14}C]penflufen at a rate of 10.7 g a.i./100 kg seed, were planted, and cotton was grown to maturity 132 days after planting. Progeny cotton seeds and cotton gin byproducts (gin trash) were collected from the mature cotton. Cotton seeds were hand-ginned to generate undelinted cottonseed. The undelinted cottonseed and cotton gin byproducts were homogenized and radio-assayed. The LLMV was 0.01 ppm in cottonseed and cotton gin byproducts. The LOD for both undelinted cottonseed and cotton gin byproducts was calculated to be 0.0012 ppm. The TRRs in undelinted cottonseed and cotton gin byproducts were <0.0012 ppm (<LOD) in all samples.	
Residue data in rotational crops	**Reference: 1886005**
Eighteen field rotational crop trials (six wheat trials in Zones 5 and 11, six turnip and six mustard green trials in Zones 2,5 and 6) were conducted in United States in 2008. 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 (2 g a.i./100 kg seed) or treated seed pieces (2 g a.i./100 kg seed) and in-furrow treatment (80 g a.i./ha). Seeds were sown at a rate of 4000 kg seed/ha for an application rate of 80 g a.i./ha for the treated seeds or 160 g a.i./ha for the combined treated seed pieces and in-furrow application. Quantifiable residues of penflufen (greater than the LOQ; 0.01 ppm) were not observed in wheat grain, forage, hay and straw, turnip roots and tops, and mustard greens at any of the three PBIs.	
Processed food and feed – potato	**Reference: 1886007**
Test Site	One trial in the United States
Treatment	Seed-piece treatment followed by in-furrow application
Rate	10 g a.i./100 kg seed + 526 g a.i./ha (= total rate of 796 g a.i./ha)
End-use product	Suspension formulation
Preharvest interval	Crop harvested at maturity
Processed commodity	**Processing Factor**
Wet peel	4.0×
Chips	Penflufen residues were <0.01 ppm in potato tubers and processed commodities (except peel). No processing factors could be derived for penflufen in these potato processed fractions.
Flakes	
Processed food and feed – corn	**Reference: 1885937**
Test Site	One trial in Canada
Treatment	Seed treatment
Rate	50 g a.i./100 kg seed
End-use product	Suspension formulation

Nature of the residue in wheat	Reference: 1886136, 1886129
Preharvest interval	Crop harvested at maturity
Processed commodity	**Processing factor**
Penflufen residues were <0.01 ppm in corn grain grown from seed treated with penflufen at an exaggerated rate. No processing factors could be determined for penflufen in corn processed fractions.	

Processed food and feed – wheat	Reference: 1885977
Processed food and feed - wheat	
Test Site	Three trials in Canada
Treatment	Seed treatment
Rate	25 g a.i./100 kg seed
End-use product	Suspension formulation
Preharvest interval	Crop harvested at maturity
Processed commodity	**Processing factor**
Penflufen residues were <0.01 ppm in wheat grain, hay and straw grown from seed treated with penflufen at an exaggerated rate. No processing factors are required for penflufen in wheat processed fractions.	

Processed food and feed – soybean	Reference: 1885939
Test Site	Three trials in Canada and the United States
Treatment	Seed treatment
Rate	25 g a.i./100 kg seed
End-use product	Suspension formulation
Preharvest interval	Crop harvested at maturity
Processed commodity	**Processing factor**
Penflufen residues were <0.01 ppm in soybean shelled immature seed, podded immature seed, mature seed and hay grown from seed treated with penflufen at an exaggerated rate. No processing factors could be determined for penflufen in wheat processed fractions.	

Livestock feeding – dairy cattle	Reference: 2026879

The magnitude of residues in dairy cow tissues and milk following dietary exposure to penflufen was determined in a feeding study. For 29 consecutive days, 14 lactating dairy cows were administered penflufen, each at a dose level of either 0 mg/kg bw/day (control; 2 cows), 0.045 mg/kg bw/day (1.41 ppm of feed; 3 cows; 1× group), 0.130 mg/kg bw/day (4.86 ppm of feed; 3 cows; 3× group) or 0.438 mg/kg bw/day (15.37 ppm in feed; 6 cows; 10× group).

Milk samples from each animal were collected at intervals during the study beginning on Day 0, on 8 days during the dosing period and on six days during the depuration phase. Ten animals were sacrificed on study day 29 (one control, three 1×, three 3× and three 10× groups) within 4 hours of the last dose. Tissue samples were taken immediately after the sacrifice of the animals. The three depuration animals of the high dose 10× group were sacrificed on study days 32, 36, and 43 to determine residue levels post-dosing. The other control group cow was also sacrificed at study day 43.

Nature of the residue in wheat	Reference: 1886136, 1886129
No residues of penflufen or penflufen-3,4'-dihydroxy were detected above the LOQ of 0.01 ppm in any milk samples from the cows from the control group or the 1×, 3× and 10× dose groups. No residues of penflufen or penflufen-3,4'-dihydroxy were detected above the LOQ of 0.01 ppm in any kidney, muscle or fat samples from the cows from the 10× dose group. In liver, residues of 0.016 ppm were observed for penflufen for the 10× dose group. No residues were detected in any milk or animal tissue sample at any stage during the depuration period. As per Regulatory Directive DIR98-02, *Residue chemistry guidelines*, there are various potential livestock feeding items resulting from crops treated with penflufen. Given that maximum residues in all crops were <0.01 ppm in the field trials as well as in corn, wheat and soybean in the processing studies carried out at exaggerated rates, no significant residues are expected in feedstuffs from the proposed use of penflufen, and there is no expectation of quantifiable residues in animal commodities.	

Table 18 Food residue chemistry overview of metabolism studies and risk assessment

Plant studies	
Residue definition for enforcement Primary crops: Rotational crops:	 Penflufen Penflufen
Residue definition for risk assessment Primary crops: Rotational crops:	 Penflufen Penflufen
Metabolic profile in diverse crops (wheat, soybean, potato, rice)	Similar
Animal studies	
Residue definition for enforcement	Penflufen
Residue definition for risk assessment	Penflufen
Metabolic profile in animals (goat, hen, rat)	Similar
Fat soluble residue	No

Dietary risk from food and water

Risk assessment	Population	Estimated risk	
		Food only	Food and water
Refined chronic non-cancer dietary risk ADI = 0.04 mg/kg bw/day Estimated chronic drinking water concentration = 30 µg a.i./L		% of acceptable daily intake (ADI)	
	All infants < 1 year	<1.0	5.5
	Children 1–2 years	<1.0	3.0
	Children 3–5 years	<1.0	2.7
	Children 6–12 years	<1.0	1.8
	Youth 13–19 years	<1.0	1.3

Plant studies			
	Adults 20–49 years	<1.0	1.6
	Adults 50+ years	<1.0	1.7
	Females 13–49 years	<1.0	1.6
	Total population	<1.0	1.8
Basic acute dietary exposure analysis, 95th percentile Estimated acute drinking water concentration = 133 µg a.i./L ARfD = 0.5 mg/kg bw		% of acute reference dose (ARfD)	
	All infants < 1 year	<1.0	5.3
	Children 1–2 years	<1.0	2.3
	Children 3–5 years	<1.0	2.1
	Children 6–12 years	<1.0	1.5
	Youth 13–19 years	<1.0	1.2
	Adults 20–49 years	<1.0	1.3
	Adults 50+ years	<1.0	1.2
	Females 13–49 years	<1.0	1.3
	Total population	<1.0	1.4
Refined chronic cancer dietary risk q_1* = 2.59×10^{-3} mg/kg bw/day Estimated chronic drinking water concentration = 30 µg a.i./L	Total population	1.9×10^{-7}	1.8×10^{-6}

Table 19 Fate and behaviour in the terrestrial and aquatic environments

Study type	Test material	Study conditions	Value or endpoint	Interpretation	Major transformation products	Reference
Abiotic transformation						
Hydrolysis	Penflufen	7-d, pH 4, 7 and 9 at 50ºC	Stable	Not a major route of transformation	n/a	1885884
Phototransformation - water	Penflufen	25ºC, pH 7	DT_{50} = 17 d (under continuous irradiation)	Not a major route of transformation	n/a	1885889
Biotransformation						
Soil -aerobic	Penflufen	120 d, four soils; pH 6.2-7.4, %OC 1.12-1.79	DT_{50} = 117 to 243 d	Moderately persistent to persistent	BYF 14182-3-hydroxy-butyl	1885893
		365d, two soils; pH 7-8; %OC 0.6-1.8	DT_{50} = 249 to 432 d	Persistent	BYF 14182-3-hydroxy-butyl and BYF 14182-pyrazolyl-AAP	1885891
	BYF 14182-pyrazolyl-AAP	122 d, four soils; pH 6.7-7.4, %OC 1.7-4.8	DT_{50} = 115 to 254 d	Moderately persistent to persistent	n/a	1885899
Soil - anaerobic	Penflufen	184 d, silt loam soil; pH 6.7; %OC 3.4	DT_{50} = 871 to 997 d	Persistent	n/a	1885895
Water/sediment - aerobic	Penflufen	120d, water:sand sediment, 19.9ºC; pH 6.8 (water)	DT_{50} = 5.9 d (water) DT_{50} = 283 d (whole system)	Persistent	n/a	1885894
Water-sediment - anaerobic	Penflufen	120d, pond water:silt clay sediment, 20ºC, pH 5.8 (water)	DT_{50} = 48.5 d (water) DT_{50} = 2190 d (whole system)	Persistent	n/a	1885892
Mobility						
Adsorption/ desorption	Penflufen	Five soils (pH 5.2-6.3, 1.2-2.3%OC)	K_{oc} = 219 to 435	Moderate to low mobility	n/a	1885885
	BYF14182-	Five soils (pH	K_{oc} = 27 to	Very high to	n/a	1885903

Study type	Test material	Study conditions	Value or endpoint	Interpretation	Major transformation products	Reference
	3-hydroxy-butyl	5.1-6.4, 0.9-2.9%OC)	63	high mobility		
	BYF 14182-pyrazolyl-AAP	Five soils (pH 4.7-7.2, 0.9-2.8%OC)	K_{oc} = 947 to 7223	Low mobility to immobile	n/a	1885898
Bioconcentration/Bioaccumulation						
Bioconcentration	Penflufen		BCF = 37.2 (edible tissue) BCF = 102 (whole fish)	Low potential to bioconcentrate	n/a	1885886
Field studies						
Field dissipation	Penflufen	Four sites relevant to Canadian conditions (Idaho, Ontario, Saskatchewan, PEI)	DT_{50} between 14 and 308 days. No radioactivity found below 15 cm in Ontario, Saskatchewan and PEI. In Idaho, penflufen was detected to a depth of 60 cm but only until day 166, after which, no radioactivity was found below 15 cm. No major transformation products were identified in the field studies.		n/a	1886211 1886212 1886221 1886218

Table 20 Toxicity to non-target species

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference
Terrestrial species							
Invertebrates	Acute oral	Honey bee (*Apis mellifera*)	Penflufen	48-h LD_{50}	>108.2 µg a.i./bee	mortality	1886098
			PEN 240FS	48-h LD_{50}	>111.7 µg a.i./bee	mortality	1885193
	Acute contact	Honey bee (*Apis mellifera*)	Penflufen	48-h LC_{50}	>100 µg a.i./bee	mortality	1886098
			PEN 240FS	48-h LC_{50}	>100 µg a.i./bee	mortality	1885193
		Earthworm (*Eisenia fetida*)	Penflufen	14-d LC_{50}	>1000 mg a.i./kg soil	mortality	1885942
		Parasitic wasp (*Aphidius rhopalosiphi*)	PEN 240FS	48-h LR_{50}	>250 g a.i./ha	mortality	1886267
		Predatory mite (*Typhlodromus pyri*)	PEN 240FS	48-h LR_{50}	>250 g a.i./ha	mortality	1886269
		Soil mite (*Hypoaspis aculeifer*)	PEN 240FS	14-d beneficial capacity	0% 0%	mortality fecundity	1885995
		Soil mite (*Hypoaspis aculeifer*)	Penflufen-3-hydroxy-butyl	14-d beneficial capacity	0% 0%	mortality fecundity	1886023
		Soil mite (*Hypoaspis aculeifer*)	Penflufen-pyrzaolyl-AAP	14-d beneficial capacity	0% 0%	mortality fecundity	1886027
	Reproduction	Earthworm (*Eisenia fetida*)	PEN 240FS	56-d NOEC	57.8 mg a.i./kg soil	reproduction	1886033
			Penflufen-3-hydroxy-butyl		>1000 mg a.i./kg soil	reproduction	1886021
			Penflufen-pyrzaolyl-AAP		500 mg a.i./kg soil	reproduction	1886028
		Predatory wasp (*Aphidius rhopalosiphi*)	PEN 240FS	NOER	124 g a.i./ha	reproduction	1886267
		Predatory mite (*Typhlodromus pyri*)	PEN 240FS	NOER	124 g a.i./ha	reproduction	1886269
Birds	Acute oral	Bobwhite quail (*Colinus virginianus*)	Penflufen	LD_{50}	>4000 mg a.i./kg bw	mortality	1886261
			PEN 240FS	LD_{50}	>456 mg a.i./kg bw	mortality	1885188

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference
		Canary (*Serinus canaria*)	Penflufen	LD_{50}	>2000 mg a.i./kg bw	mortality	1886257
	Dietary	Bobwhite quail (*Colinus virginianus*)	Penflufen	LC_{50}	>8944 mg a.i./kg diet	mortality	1886260
		Mallard duck (*Anas platyrhynchos*)	Penflufen	LC_{50}	>9923 mg a.i./kg diet	mortality	1886258
	Chronic	Bobwhite quail (*Colinus virginianus*)	Penflufen	NOEC	946 mg a.i./kg diet	reproduction	1886262
		Mallard duck (*Anas platyrhynchos*)	Penflufen	NOEC	<292 mg a.i./kg diet	reproduction	1886263
Mammals	Acute oral	Rat	Penflufen	LD_{50}	>2000 mg a.i./kg bw	mortality	1885952
	Dietary	Rat	Penflufen	NOEL	949 mg a.i./kg diet	growth	1885944
	Chronic (2-generation)	Rat	Penflufen	NOEL	75.9 mg a.i./kg bw	reproduction	1886198
Plants	Seedling emergence	11 plant species	PEN 240FS	EC_{25}	>250 g a.i. /ha	length	1885991
	Vegetative vigour				>250 g a.i. /ha	weight	1885992
Freshwater Organisms							
Invertebrates	Acute	*Daphnia magna*	Penflufen	48-h EC_{50}	>4.66 mg a.i./L	immobility	1885909
			PEN 240FS	48-h EC_{50}	4.928 mg a.i./L		1885191
			Penflufen-3-hydroxy-butyl	48-h EC_{50}	>62 mg a.i./L		1885913
			Penflufen-pyrazolyl-AAP	48-h EC_{50}	>3.12 mg a.i./L		1885914
		Crayfish (*Procambarus clarkia*)	Penflufen	96-h EC_{50}	>4.5 mg a.i./L		1885908
	Chronic	*Daphnia magna*	Penflufen	21-d NOEC	1.53 mg a.i./L		1886045
		Chironomus dilutus	Penflufen	10-d NOEC	0.78 mg a.i./L	reproduction	1886192
Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	Penflufen	96-h LC_{50}	0.31 mg a.i./L	mortality	1885911
		Bluegill sunfish (*Lepomis macrochirus*)	Penflufen	96-h LC_{50}	0.45 mg a.i./L	mortality	1885907
		Fathead minnow	Penflufen	96-h LC_{50}	0.116 mg	mortality	1885910

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference
		(*Pimephales promelas*)			a.i./L		
		Common carp (*Cyprinus carpio*)	Penflufen	96-h LC_{50}	0.090 mg a.i./L	mortality	1885906
			PEN 240FS	96-h LC_{50}	>0.101 mg a.i./L	mortality	1885189
			Penflufen-3-hydroxy-butyl	96-h LC_{50}	>36.3 mg a.i./L	mortality	1885915
			Penflufen-pyrazolyl-AAP	96-h LC_{50}	>0.799 mg a.i./L	mortality	1885916
	Chronic (early life stage)	Fathead minnow (*Pimephales promelas*)	Penflufen	35-d NOEC	0.0234 mg a.i./L	growth	1886096
Algae	Acute	Green alga (*Pseudokirchneriella subcapitata*)	Penflufen	EC_{50}	>5.1 mg a.i./L	growth and reproduction	1886265
			PEN 240FS		7.5 mg a.i./L		1885192
			Penflufen-3-hydroxy-butyl		>1071.5 mg a.i./L		1886186
			Penflufen-pyrazolyl-AAP		>60.8 mg a.i./L		1886266
Vascular plants	Acute	Duckweed (*Lemna gibba*)	Penflufen	7-d EC_{50} NOEC	>4.7 mg a.i./L 2.4 mg a.i./L		1886264
Marine/Estuarine organisms							
Invertebrates	Acute	Mysid shrimp (*Americamysis bahia*)	Penflufen	96-h LC_{50}	2.5 mg a.i./L	mortality	1886031
		Eastern oyster (*Crassostrea virginica*)		96-h LC_{50}	1.3 mg a.i./L	shell deposition	1886030
Fish	Acute	Sheepshead minnow (*Cyprinodon variegates*)	Penflufen	96-h LC_{50}	1.15 mg a.i./L	mortality	1885912

Table 21 Screening level risk to terrestrial invertebrates

Organism	Exposure	Test substance	Endpoint value	EEC[a] (mg a.i./kg)	RQ[b]
Earthworm	Acute	Penflufen	½ LC_{50}: > 500 mg a.i./kg dw	0.0711	<0.1
	Reproduction	Pen 240FS	NOEC: 57.8 mg a.i./kg dw	0.0711	<0.1
Soil mite	Contact	Pen 240FS	½ LR_{50}: > 1000 mg a.i./kg dw	0.0711	<0.1

[a] Estimated Environmental Concentration (Soil: calculated based on a soil density of 1.5 g/cm^3, soil depth of 15 cm and the maximum label rate for potatoes.

[b] Risk Quotient (RQ) = exposure/toxicity. RQ > 1 indicates exceedance of LOC (Level Of Concern)

Table 22 Screening level risk to birds and small wild mammals based on canola seed

Generic body weight of organism (kg)	Exposure (# seeds/d)[1]	Toxicity (# seeds/d)[2]	RQ[3]
Birds			
0.02	1692	**Acute:** >13333	<0.1
		Dietary: 5657	0.3
		Reproduction: 900	1.9
0.1	6627	**Acute:** >66667	<0.1
		Dietary: 28283	0.2
		Reproduction: 4500	1.5
1	19347	**Acute:** >666667	<0.1
		Dietary: 282833	0.1
		Reproduction: 45000	0.4
Mammals			
0.015	726	**Acute:** >12500	<0.1
		Dietary: 23650	<0.1
		Reproduction: 1898	0.4
0.035	1455	**Acute:** >29167	<0.1
		Dietary: 55183	<0.1
		Reproduction: 4428	0.3
1	22877	**Acute:** >833333	<0.1
		Dietary: 1576667	<0.1
		Reproduction: 126500	0.2

Note: Shaded cells indicate that the RQ exceeds the level of concern (LOC = 1)

[a] Estimated exposure calculated as # seeds/g × FIR, where FIR is the food ingestion rate calculated using the following equations:

For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used:
FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$

For generic birds with body weight greater than 200 g, the "all birds" equation was used:
FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$

[b] Number of seeds to reach endpoint calculated as Daily dose (mg a.i./kg bw or mg a.i./kg bw/day) × generic body weight of organism (kg) ÷ Amount of active ingredient per seed (mg a.i./seed), where the amount of a.i. per seed = seed treatment rate (g a.i./kg seed) / # seeds/kg and was calculated to be 0.0006 mg penflufen per seed.

[c] Risk quotient (RQ) = exposure/toxicity. Shaded cells indicate that the RQ exceeds the level of concern (LOC =1)

Table 23 Screening level risk of penflufen to aquatic organisms

Organism	Exposure	Endpoint value[a] (mg a.i./L)	EEC[b] (mg a.i./L)	RQ[c]
Freshwater species				
Freshwater crustacean	Acute	½ EC_{50}: >2.25	0.0132	<0.1
Freshwater midge	Chronic	NOEC: 0.78	0.0132	<0.1
Common carp	Acute	1/10 LC_{50}: 0.009	0.0132	1.5
Fathead minnow	ELS	NOEC: 0.0234	0.0132	0.6
Amphibian	Fish Acute	1/10 LC_{50}: 0.009	0.0704	7.8
	Fish ELS	NOEC: 0.0243	0.0704	3.0
Freshwater alga	Acute	½ EC_{50}: >2.55	0.0132	<0.1
Vascular plant	Dissolved	½ EC_{50}: 2.35	0.0132	<0.1
Marine species				
Mollusk	Acute	½ LC_{50}: 0.65	0.0132	<0.1
Sheepshead minnow	Acute	1/10 LC_{50}: 0.115	0.0132	0.1
Shaded cells indicate that the RQ exceeds the level of concern (LOC =1)				

[a] Endpoints used in the acute exposure risk assessment are derived by diving the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.

[b] Estimated Environmental Concentration (EEC) based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms. Application rate based on a single in-furrow application rate (105.6 g a.i./ha).

[c] Risk Quotient (RQ) = exposure/toxicity. RQ > 1 indicates exceedance of LOC (Level Of Concern)

Table 24 Level I risk of penflufen to freshwater aquatic organisms exposed to predicted run-off

Organism	Exposure	Endpoint value[a] (mg a.i./L)	Level I EEC[b] (mg a.i./L)	RQ[c]
Common carp	Acute	1/10 LC_{50}: 0.009	0.0023	0.3
Amphibian	Fish Acute	1/10 LC_{50}: 0.009	0.0078	0.9
	Fish ELS	NOEC: 0.0243	0.0054	0.2

[a] Endpoints used in the acute exposure risk assessment are derived by diving the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.

[b] 90^{th} percentile of peak and 21-d run-off values for acute and chronic exposure, respectively

[c] Risk Quotient (RQ) = exposure/toxicity. RQ > 1 indicates exceedance of LOC (Level Of Concern)

Table 25 Summary of fungicide alternatives

Crop	Pests	Active ingredient (and resistance management group)
Uses supported with PEN 240FS and PENRED 240FS		
Canola	Seed rot / pre-emergence damping-off , post-emergence damping-off (soil-borne *Rhizoctonia solani*)	iprodione (2) + thiram (M3) difenoconazole (3) + metalaxyl (4) + fludioxonil (12) metalaxyl (4) + carbathiin (7) + trifloxystrobin (11) metalaxyl (4) + carbathiin (7) + thiram (M3) carbathiin (7) + thiram (M3) trifloxystrobin (11) *Bacillus subtilis* (44)
	Seed rot / pre-emergence damping-off (soil-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) + fludioxonil (12) metalaxyl (4) + carbathiin (7) + trifloxystrobin (11) metalaxyl (4) + carbathiin (7) + thiram (M3) *Bacillus subtilis* (44)
Rapeseed	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne Rhizoctonia solani)	metalaxyl (4) + carbathiin (7) + thiram (M3) carbathiin (7) + thiram (M3) trifloxystrobin (11)
	Seed rot / pre-emergence damping-off (soil-borne *Fusarium* spp.)	metalaxyl (4) + carbathiin (7) + thiram (M3)
Mustard	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Rhizoctonia solani*)	iprodione (2) + thiram (M3) difenoconazole (3) + metalaxyl (4) + fludioxonil (12) carbathiin (7) + thiram (M3) trifloxystrobin (11) fludioxonil (12)
	Seed rot / pre-emergence damping-off (soil-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) + fludioxonil (12)
Flax	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Rhizoctonia solani*)	carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off (soil-borne *Fusarium* spp.)	carbathiin (7) + thiram (M3)
Cramba	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Rhizoctonia solani*)	n/a
	Seed rot / pre-emergence damping-off (soil-borne *Fusarium* spp.)	n/a

Crop	Pests	Active ingredient (and resistance management group)
Borage	Seed rot / pre-emergence damping-off , post-emergence damping-off (soil-borne *Rhizoctonia solani*)	n/a
	Seed rot / pre-emergence damping-off (soil-borne *Fusarium* spp.)	n/a
Sunflower	Seedling blight (soil-borne *Rhizoctonia solani*)	n/a
Safflower	Seedling blight (soil-borne *Rhizoctonia solani*)	n/a
Beans and peas	Seed rot / pre-emergence damping-off, post-emergence damping-off, early-season root rot (soil-borne *Rhizoctonia solani*, *Fusarium* spp.)	metalaxyl (4) + trifloxystrobin (11) metalaxyl (4) + fludioxonil (12) carbathiin (7) + thiram (M3) azoxystrobin (11) trifloxystrobin (11) *Trichoderma harzianum* (NC)
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Botrytis cinerea*)	metalaxyl (4) + fludioxonil (12) trifloxystrobin (11)
Wheat	Loose smut (*Ustilago tritici*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) triadimenol (3) triticonazole (3) carbathiin (7) carbathiin (7) + thiram (M3)
	Common bunt (*Tilletia caries*, *Tilletia laevis*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) maneb (M3)

Crop	Pests	Active ingredient (and resistance management group)
Barley	True loose smut (*Ustilago nuda*)	ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3)
	False loose smut (*Ustilago nigra*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) maneb (M3) mancozeb (M3)
	Covered smut (*Ustilago hordei*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) maneb (M3) mancozeb (M3)

Crop	Pests	Active ingredient (and resistance management group)
	Leaf stripe (*Pyrenophora graminea*)	ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) triticonazole (3) carbathiin (7) carbathiin (7) + thiram (M3)
Oat	Loose smut (*Ustilago avenae*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) mancozeb (M3)
	Covered smut (*Ustilago kolleri*)	ipconazole (3) difenoconazole (3) + metalaxyl (4) tebuconazole (3) + metalaxyl (4) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) + thiram (M3) maneb (M3) mancozeb (M3)
Winter wheat	Pink snow mould (*Monographella nivalis*)	n/a
Rye	Stem smut (*Urocystis occulta*)	carbathiin (7) carbathiin (7) + thiram (M3)
Corn	Seed rot / pre-emergence damping-off (soil-borne *Rhizoctonia solani*)	thiabendazole (1) + metalaxyl (4) + azoxystrobin (11) + fludioxonil (12) ipconazole (3) metalaxyl (4) + fludioxonil (12) azoxystrobin (11)
Sorghum	Seed rot / pre-emergence damping-off (soil-borne *Rhizoctonia solani*)	n/a
Alfalfa	Seed rot / pre-emergence damping-off (soil-borne *Rhizoctonia solani*)	fludioxonil (12)* *non-grass animal feeds only

Crop	Pests	Active ingredient (and resistance management group)
Potatoes	Black scurf (*Rhizoctonia solani*)	thiophanate-methyl (1) + mancozeb (M3) iprodione (2) azoxystrobin (11) fludioxonil (12) fludioxonil (12) + mancozeb (M3) formalin (U) saponins of *Chenopodium quinoa* (NC)
	Silver scurf (*Helminthosporium solani*)	thiophanate-methyl (1) iprodione (2) azoxystrobin (11) fludioxonil (12) fludioxonil (12) + mancozeb (M3) phosphorous acid (33) *Bacillus subtilis* (44)
Uses supported with PENPRO 118FS		
Potatoes	Black scurf (*Rhizoctonia solani*)	thiophanate-methyl (1) + mancozeb (M3) iprodione (2) azoxystrobin (11) fludioxonil (12) fludioxonil (12) + mancozeb (M3) formalin (U) saponins of *Chenopodium quinoa* (NC)
	Silver scurf (*Helminthosporium solani*)	thiophanate-methyl (1) iprodione (2) azoxystrobin (11) fludioxonil (12) fludioxonil (12) + mancozeb (M3) phosphorous acid (33) *Bacillus subtilis* (44)
	Fusarium tuber rot (*Fusarium* spp.)	thiophanate-methyl (1) thiophanate-methyl (1) + mancozeb (M3) fludioxonil (12) fludioxonil (12) + mancozeb (M3) mancozeb (M3) metiram (M3) chloropicrin (F)
Uses supported with PENCLO 273.5FS		

Crop	Pests	Active ingredient (and resistance management group)
Potatoes	Black scurf (*Rhizoctonia solani*)	thiophanate-methyl (1) + mancozeb (M3) iprodione (2) azoxystrobin (11) fludioxonil (12) fludioxonil (12) + mancozeb (M3) formalin (U) saponins of *Chenopodium quinoa* (NC)
	Silver scurf (*Helminthosporium solani*)	thiophanate-methyl (1) iprodione (2) azoxystrobin (11) fludioxonil (12) fludioxonil (12) + mancozeb (M3) phosphorous acid (33) *Bacillus subtilis* (44)
Uses supported with PENTRI 308FS		
Beans and Peas	Seed rot / pre-emergence damping-off, post-emergence damping-off (*Rhizoctonia solani*, *Fusarium* spp.)	metalaxyl (4) + trifloxystrobin (11) metalaxyl (4) + fludioxonil (12) carbathiin (7) + thiram (M3) azoxystrobin (11) trifloxystrobin (11) *Trichoderma harzianum* (NC)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight (seed-borne *Botrytis cinerea*)	metalaxyl (4) + fludioxonil (12) trifloxystrobin (11)
	Seed rot / pre-emergence damping-off of soybean (seed-borne *Phomopsis longicolla*)	metalaxyl (4) + trifloxystrobin (11) metalaxyl (4) + fludioxonil (12) thiamethoxam (4) + metalaxyl (4) + fludioxonil (12) carbathiin (7) + thiram (M3)
Corn	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Rhizoctonia solani*)	thiabendazole (1) + metalaxyl (4) + azoxystrobin (11) + fludioxonil (12) ipconazole (3) metalaxyl (4) + fludioxonil (12) azoxystrobin (11)
	Seed rot / pre-emergence damping-off, post-emergence damping-off (*Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) trifloxystrobin (11) trifloxystrobin (11) + metalaxyl (4) fludioxonil (12) + metalaxyl (4)

Crop	Pests	Active ingredient (and resistance management group)
Alfalfa	Seed rot / pre-emergence damping-off (soil-borne *Rhizoctonia solani*)	fludioxonil (12)* *non-grass animal feeds only
Uses supported with PENCLOTRIME 310.68FS		
Canola	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Rhizoctonia solani*)	iprodione (2) + thiram (M3) difenoconazole (3) + metalaxyl (4) + fludioxonil (12) metalaxyl (4) + carbathiin (7) + trifloxystrobin (11) metalaxyl (4) + carbathiin (7) + thiram (M3) carbathiin (7) + thiram (M3) trifloxystrobin (11) *Bacillus subtilis* (44)
	Seed rot / pre-emergence damping-off , post-emergence damping-off (soil-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) + fludioxonil (12) metalaxyl (4) + carbathiin (7) + trifloxystrobin (11) metalaxyl (4) + carbathiin (7) + thiram (M3) *Bacillus subtilis* (44)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, early-season root rot (soil-borne *Pythium* spp.)	difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) + fludioxonil (12) difenoconazole (3) + metalaxyl (4) + fludioxonil (12) metalaxyl (4) + carbathiin (7) + trifloxystrobin (11) metalaxyl (4) + carbathiin (7) + thiram (M3) carbathiin (7) + thiram (M3)
Rapeseed	Seed rot / pre-emergence damping-off , post-emergence damping-off (soil-borne *Rhizoctonia solani*)	metalaxyl (4) + carbathiin (7) + thiram (M3) carbathiin (7) + thiram (M3) trifloxystrobin (11)
	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Fusarium* spp.)	metalaxyl (4) + carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, early-season root rot (soil-borne *Pythium* spp.)	metalaxyl (4) + carbathiin (7) + thiram (M3) carbathiin (7) + thiram (M3)

Crop	Pests	Active ingredient (and resistance management group)
Mustard	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Rhizoctonia solani*)	iprodione (2) + thiram (M3) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) + fludioxonil (12) difenoconazole (3) + metalaxyl (4) + fludioxonil (12) carbathiin (7) + thiram (M3) trifloxystrobin (11) fludioxonil (12)
	Seed rot / pre-emergence damping-off, post-emergence damping-off (soil-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) + fludioxonil (12) difenoconazole (3) + metalaxyl (4) + fludioxonil (12) fludioxonil (12)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight and early-season root rot (soil-borne *Pythium* spp.)	difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) + fludioxonil (12) difenoconazole (3) + metalaxyl (4) + fludioxonil (12) carbathiin (7) + thiram (M3)
Uses supported with PENPROME 177FS		
Wheat	Loose smut (*Ustilago tritici*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) triadimenol (3) triticonazole (3) carbathiin (7) carbathiin (7) + thiram (M3)
	Common bunt (*Tilletia caries*, *Tilletia laevis*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) maneb (M3)

Crop	Pests	Active ingredient (and resistance management group)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, root and suppression of crown rot (seed-borne *Fusarium* spp.)	tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triticonazole (3) triticonazole (3) + thiram (M3) difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) carbathiin (7) + thiram (M3) fludioxonil (12)
	Seed rot / pre-emergence damping-off, seedling blight, suppression of root rot (seed-borne *Cochliobolus sativus*)	triticonazole (3) triticonazole (3) + thiram (M3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Aspergillus* spp.)	difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) carbathiin (7) + thiram (M3)
	Suppression of seedling blight (seed-borne *Penicillium* spp.)	carbathiin (7) + thiram (M3)
Winter wheat	Pink snow mould (*Monographella nivalis*)	n/a
Barley	True loose smut (*Ustilago nuda*)	ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3)

Crop	Pests	Active ingredient (and resistance management group)
	False loose smut (*Ustilago nigra*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) maneb (M3) mancozeb (M3)
	Covered smut (*Ustilago hordei*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triadimenol (3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) maneb (M3) mancozeb (M3)
	Leaf stripe (*Pyrenophora graminea*)	ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) triticonazole (3) carbathiin (7) carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, suppression of root and crown rot (seed-borne *Fusarium* spp.)	tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triticonazole (3) triticonazole (3) + thiram (M3) difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) carbathiin (7) + thiram (M3) fludioxonil (12)

Crop	Pests	Active ingredient (and resistance management group)
	Seed rot / pre-emergence damping-off, seedling blight, suppression of root rot (seed-borne *Cochliobolus sativus*)	difenoconazole (3) + metalaxyl (4) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + metalaxyl (4) + thiamethoxam (4) tebuconazole (3) + thiram (M3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Aspergillus* spp.)	difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) carbathiin (7) + thiram (M3)
	Suppression of seedling blight (seed-borne *Penicillium* spp.)	carbathiin (7) + thiram (M3)
Oat	Loose smut (*Ustilago avenae*)	difenoconazole (3) + metalaxyl (4) ipconazole (3) tebuconazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) carbathiin (7) + thiram (M3) mancozeb (M3)
	Covered smut (*Ustilago kolleri*)	ipconazole (3) difenoconazole (3) + metalaxyl (4) tebuconazole (3) + metalaxyl (4) triticonazole (3) triticonazole (3) + thiram (M3) carbathiin (7) + thiram (M3) maneb (M3) mancozeb (M3)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, suppression of root and crown rot (seed-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) triticonazole (3) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) carbathiin (7) + thiram (M3) fludioxonil (12)

Crop	Pests	Active ingredient (and resistance management group)
	Seed rot / pre-emergence damping-off, seedling blight, suppression of root rot (seed-borne *Cochliobolus sativus*)	difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) tebuconazole (3) + metalaxyl (4) tebuconazole (3) + thiram (M3) triticonazole (3) carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Aspergillus* spp.)	difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) carbathiin (7) + thiram (M3)
	Suppression of seedling blight (seed-borne *Penicillium* spp.)	carbathiin (7) + thiram (M3)
Rye	Stem smut (*Urocystis occulta*)	carbathiin (7) carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, suppression of root and crown rot (seed-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) carbathiin (7) + thiram (M3) fludioxonil (12)
	Seed rot / pre-emergence damping-off, seedling blight, suppression of root rot (seed-borne *Cochliobolus sativus*)	difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Aspergillus* spp.)	difenoconazole (3) + metalaxyl (4) difenoconazole (3) + metalaxyl (4) + thiamethoxam (4) carbathiin (7) + thiram (M3)
	Suppression of seedling blight caused by seed-borne *Penicillium* spp.	carbathiin (7) + thiram (M3)
Triticale	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, suppression of root and crown rot (seed-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4) fludioxonil (12)
	Seed rot / pre-emergence damping-off, seedling blight, suppression of root rot (seed-borne *Cochliobolus sativus*)	difenoconazole (3) + metalaxyl (4)
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Aspergillus* spp.)	difenoconazole (3) + metalaxyl (4)
	Suppression of seedling blight (seed-borne *Penicillium* spp.)	difenoconazole (3) + metalaxyl (4)

Crop	Pests	Active ingredient (and resistance management group)
Millet	Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight, suppression of root and crown rot (seed-borne *Fusarium* spp.)	difenoconazole (3) + metalaxyl (4)
	Seed rot / pre-emergence damping-off, seedling blight, suppression of root rot (seed-borne *Cochliobolus* sativus)	n/a
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Aspergillus* spp.)	difenoconazole (3) + metalaxyl (4)
Corn (field, sweet, popcorn)	Suppression of seedling blight (seed-borne *Penicillium* spp.)	difenoconazole (3) + metalaxyl (4) metalaxyl (4) + trifloxystrobin (11) trifloxystrobin (11)
	Seed rot / pre-emergence damping-off (soil-borne *Pythium* spp.)	azoxystrobin (11)
	Seed rot / pre-emergence damping-off (*Rhizoctonia solani*)	metalaxyl (4) + fludioxonil (12) azoxystrobin (11)
	Seed rot / pre-emergence damping-off (seed-borne *Cladosporium* spp.)	n/a
	Seed rot / pre-emergence damping-off (seed-borne *Aspergillus* spp.)	difenoconazole (3) + metalaxyl (4) metalaxyl (4) + fludioxonil (12)
	Suppression of seed rot / pre-emergence damping-off (*Penicillium* spp.)	difenoconazole (3) + metalaxyl (4) metalaxyl (4) + fludioxonil (12)
Dry shelled peas and beans, including soybean	Seed rot / pre-emergence damping-off (*Rhizoctonia solani*, *Fusarium* spp., *Pythium* spp.)	carbathiin (7) + thiram (M3) azoxystrobin (11) trifloxystrobin (11) trifloxystrobin (11) + metalaxyl (4) + fludioxonil (12) + *Trichoderma harzianum* (NC)
	Early-season root rot and seedling blight (*Rhizoctonia solani*, *Fusarium* spp.)	carbathiin (7) + thiram (M3) azoxystrobin (11) *Trichoderma harzianum* (NC)
	Seed rot / pre-emergence damping-off, seedling blight (seed-borne *Botrytis cinerea*)	metalaxyl (4) + fludioxonil (12) trifloxystrobin (11)

Crop	Pests	Active ingredient (and resistance management group)
	Seed rot / pre-emergence damping-off of soybean (seed-borne *Phomopsis longicolla*)	metalaxyl (4) + trifloxystrobin (11) metalaxyl (4) + fludioxonil (12) thiamethoxam (4) + metalaxyl (4) + fludioxonil (12) carbathiin (7) + thiram (M3)
	Seed rot / pre-emergence damping-off of chickpea (seed-borne *Ascochyta rabiei*)	thiabendazole (1) + carbathiin (7) metalaxyl (4) + trifloxystrobin (11) metalaxyl (4) + fludioxonil (12)

Table 26 Toxic Substances Management Policy considerations – comparison to TSMP Track 1 criteria

TSMP Track 1 criteria	TSMP Track 1 criterion value		Active ingredient endpoints
CEPA toxic or CEPA toxic equivalent[a]	Yes		Yes
Predominantly anthropogenic[b]	Yes		Yes
Persistence[c]:	Soil	Half-life ≥ 182 days	Half-life = 117 to 243 days
	Water	Half-life ≥ 182 days	Half-life = 6 days
	Sediment	Half-life ≥ 365 days	Half-life = 283 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (1.2×10^{-6} Pa) and Henry's law constant (1.78×10^{-10}).
Bioaccumulation[d]	Log $K_{OW}\geq 5$		3.3
	BCF ≥ 5000		103
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[a] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[b] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[c] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[d] Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{OW}).

Table 27 Use (label) claims proposed by applicant and whether acceptable or unsupported

Proposed claim	Supported / unsupported
PEN 240FS and PENRED 240FS	
Control of seed rot / pre-emergence damping-off, post-emergence damping-off caused by soil-borne *Rhizoctonia solani*; 62.5 mL/100 kg seed on canola, rapeseed, mustard (oilseed and condiment), flax (linseed), crambe, borage	Supported as proposed.
Control of seed rot / pre-emergence damping-off caused by soil-borne *Fusarium* spp.; 62.5 mL/100 kg seed on canola, rapeseed, mustard (oilseed and condiment), flax (linseed), crambe, borage	Supported as proposed.
Control of seed rot / pre-emergence damping-off caused by *Rhizoctonia solani*; 21 mL/100 kg seed on sunflower, safflower	Not supported. There was a lack of significant difference in stand establishment and no yield data in the two field trials on sunflower.
Control of seedling blight caused by soil-borne *Rhizoctonia solani*; 21 mL/100 kg seed on sunflower, safflower	Conditionally supported.
Tank-mix with Allegiance FL at labelled rates on canola, rapeseed, oilseed mustard, flax, linseed, sunflower, safflower, crambe, borage	Supported on canola, rapeseed and sunflower.
Control of seed rot / pre-emergence damping-off and post-emergence damping-off caused by soil-borne *Rhizoctonia solani* and *Fusarium* spp.; 21 mL/100 kg seed on legume vegetables	Supported as proposed.
Control of early-season root rot caused by soil-borne *Rhizoctonia solani* and *Fusarium* spp.; 21 mL/100 kg seed on legume vegetables	Supported as proposed.
Control of seed rot / pre-emergence damping-off caused by seed-borne *Botrytis cinerea*; 21 mL/100 kg seed on legume vegetables	Conditionally supported.
Control of seedling blight caused by seed-borne *Botrytis cinerea*; 21 mL/100 kg seed on legume vegetables	Supported as proposed.
Tank-mix with Allegiance FL at labelled rates on bean (succulent, snap and dry), chickpea, lentil, pea (dry and field), soybean, soybean (immature seed)	Supported as proposed.
Control of loose smut (*Ustilago tritici*, *Ustilago avenae*); 21 mL/100 kg seed on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Supported on wheat, barley, oats, rye and triticale.
Control of common bunt (*Tilletia caries*, *Tilletia laevis*); 21 mL/100 kg seed on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Supported on wheat, barley, oats, rye and triticale.
Control of true loose smut (*Ustilago nuda*); 21 mL/100 kg seed on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Supported on wheat, barley, oats, rye and triticale.
Control of false loose smut of barley (*Ustilago nigra*); 21 mL/100 kg seed on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Conditionally supported on wheat, barley, oats, rye and triticale.
Control of covered smut of barley and oat (*Ustilago hordei*, *Ustilago kolleri*); 21 mL/100 kg seed on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Conditionally supported on wheat, barley, oats, rye and triticale.

Proposed claim	Supported / unsupported
Control of leaf stripe (*Pyrenophora graminea*); 21 mL/100 kg seed on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Supported on wheat, barley, oats, rye and triticale.
Control of stem smut (*Urocystis occulta*); 21 mL/100 kg seed on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Supported on wheat, barley, oats, rye and triticale.
Suppression of seed-borne *Cochliobolus sativus* on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale	Not supported. The product efficacy was not tested in field conditions on the seedling diseases caused by seed-borne *C. sativus.*
Tank-mix with Allegiance FL at labelled rates on wheat, barley, oats, buckwheat, millet (pearl and proso), rye, triticale, teosinte	Supported on wheat, barley, oats and rye.
Suppression of pink snow mould (*Monographella nivalis*; 21 mL/100 kg seed on winter wheat	Supported as proposed.
Control of seed rot / pre-emergence damping-off caused by soil-borne *Rhizoctonia solani*; 10.5-21 mL/100 kg seed on corn (field, sweet, popcorn) and sorghum	Supported as proposed.
Tank-mix with Allegiance FL at labelled rates on corn (field, sweet, popcorn) and sorghum	Supported on corn (field, sweet) and sorghum.
Seed-borne black scurf (including stem and stolon canker) caused by *Rhizoctonia solani*; 8.5 mL/100 kg seed on potatoes	Supported as proposed.
Silver scurf caused by *Helminthosporium solani*; 8.5 mL/100 kg seed on potatoes	Supported as proposed.
Soil-borne black scurf (including stem and stolon canker) caused by *Rhizoctonia solani*; 4 mL/100 m row as an in-furrow application	Supported as proposed.
Tank-mix with Titan ST Insecticide at labelled rates on potatoes.	Supported as proposed.
Seed rot / pre-emergence damping-off caused by soil-borne *Rhizoctonia solani*; 42-62.5 mL/100 kg seed on alfalfa	Conditionally supported.
PENPRO 118FS	
Seed-borne black scurf and stem and stolon canker caused by *Rhizoctonia solani*; 20 mL/100 kg seed on potatoes	Supported as proposed.
Silver scurf caused by *Helminthosporium solani*; 20 mL/100 kg seed on potatoes	Supported as proposed.
Fusarium tuber rot caused by *Fusarium* spp.; 20 mL/100 kg seed on potatoes	Supported as proposed.
Tank-mix with Titan ST Insecticide at labelled rates on potatoes.	Supported as proposed.
PENCLO 273.5FS	
Seed-borne black scurf and stem and stolon canker caused by *Rhizoctonia solani*; 30 mL/100 kg seed on potatoes	Supported as proposed.
Silver scurf caused by *Helminthosporium solani*; 30 mL/100 kg seed on potatoes	Supported as proposed.

Proposed claim	Supported / unsupported
Colorado potato beetle; 30 mL/100 kg seed on potatoes	Supported as proposed.
Aphids; 30 mL/100 kg seed on potatoes	Supported as proposed.
Leafhopper; 30 mL/100 kg seed on potatoes	Supported as proposed.
Potato flea beetle; 30 mL/100 kg seed on potatoes	Supported as proposed.
Tank-mix of PENCLO 273.5FS (30 mL/100 kg seed) with Titan ST Insecticide (10.4 mL/100 kg seed) for suppression of damage caused by wireworms and for extended residual control of insect pests other than wireworm.	Supported as proposed.
PENTRI 308FS	
Seed decay / pre-emergence damping-off and post-emergence damping-off caused by *Rhizoctonia solani* and *Fusarium* spp.; 25 mL/100 kg seed on legume vegetables	Supported as proposed.
Seed decay / pre-emergence damping-off and post-emergence damping-off caused by seed-borne *Botrytis cinerea*; 25 mL/100 kg seed on legume vegetables	Conditionally supported.
Seedling blight caused by seed-borne *Botrytis cinerea*; 25 mL/100 kg seed on legume vegetables	Supported as proposed.
Seed decay / pre-emergence damping-off of soybean caused by seed-borne *Phomopsis longicolla*; 25 mL/100 kg seed on legume vegetables	Supported as proposed.
Suppression of seed-borne anthracnose caused by *Anthracnose* spp.; 25 mL/100 kg seed on legume vegetables	Not supported. No field trials were conducted on seed-borne anthracnose and seed-borne ascochyta blight on legume vegetables. Must be tested in the field to verify its efficacy under conditions representative of those found in Canada.
Suppression of seed-borne ascochyta blight caused by *Ascochyta* spp.; 25-32 mL/100 kg seed on legume vegetables	
Tank-mix with Allegiance FL at labelled rates on pea (dry and field), chickpea, lentil, bean (succulent, snap and dry) and soybean	Supported as proposed.
Tank-mix with Gaucho 480 FL at labelled rates on bean (succulent, snap and dry)	Supported as proposed.
Tank-mix with Stress Shield at labelled rates on bean (succulent, snap and dry)	Not supported. The proposed crops are not present on the Stress Shield label.
Tank-mix with Stress Shield at labelled rates on soybean	Supported as proposed.
Seed decay / pre-emergence damping-off and post-emergence damping-off caused by *Rhizoctonia solani*; 16-32 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Seed decay / pre-emergence damping-off caused by *Fusarium* spp.; 16-32 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Tank-mix with Allegiance FL at labelled rates on corn	Supported as proposed.

Proposed claim	Supported / unsupported
Tank-mix with Poncho 600 FS at labelled rates on corn	Supported as proposed.
Seed decay / pre-emergence damping-off caused by *Rhizoctonia solani*; 64 mL/100 kg seed on alfalfa	Conditionally supported.
Tank-mix with Allegiance FL at labelled rates on alfalfa	Supported as proposed.
PENCLOTRIME 310.68FS	
Seed rot / pre-emergence damping-off and post-emergence damping-off caused by soil-borne *Rhizoctonia solani* and *Fusarium* spp.; 1.4 L/100 kg seed on canola, rapeseed, mustard (oilseed and condiment)	Supported as proposed.
Seedling blight caused by *Rhizoctonia solani* and *Fusarium* spp.; 1.4 L/100 kg seed on canola, rapeseed, mustard (oilseed and condiment)	Not supported. No efficacy data were provided by the applicant.
Seed rot / pre-emergence damping-off, post-emergence damping-off, seedling blight and early-season root rot caused by soil-borne *Pythium* spp.; 1.4 L/100 kg seed on canola, rapeseed, mustard (oilseed and condiment)	Supported as proposed.
Seed-borne *Alternaria* spp.; 1.4 L/100 kg seed on canola, rapeseed, mustard (oilseed and condiment)	Not supported. Two laboratory bioassays on each of the two seed-borne diseases are not considered sufficient to support the corresponding claims. Must be tested in the field to verify its efficacy under conditions representative of those found in Canada.
Seed-borne blackleg (*Phoma lingam*); 1.4 L/100 kg seed on canola, rapeseed, mustard (oilseed and condiment)	
Flea beetles 1.4 L/100 kg seed on canola, rapeseed, mustard (oilseed and condiment)	Supported as proposed.
PENPROME 177FS	
Loose smut (*Ustilago tritici*, *Ustilago avenae*); 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Common bunt (*Tilletia caries*, *Tilletia laevis*); 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
True loose smut (*Ustilago nuda*); 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
False loose smut (*Ustilago nigra*); 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Covered smut (*Ustilago hordei*, *Ustilago kolleri*); 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Leaf stripe (*Pyrenophora graminea*); 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Stem smut (*Urocystis occulta*); 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Conditionally supported.

Proposed claim	Supported / unsupported
Seed rot / pre-emergence damping-off and seedling blight caused by seed-borne *Fusarium* spp. and *Cochliobolus sativus*; 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Post-emergence damping-off caused by soil-borne *Fusarium* spp.; 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Seed rot / pre-emergence damping-off, and post-emergence damping-off and seedling blight caused by seed-borne *Aspergillus* spp.; 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Suppression of root rot caused by seed-borne and soil-borne *Fusarium* spp.; 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Suppression of root rot caused by soil-borne *Cochliobolus sativus*; 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Suppression of crown rot caused by seed-borne *Fusarium* spp.; 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Suppression of seedling blight caused by seed-borne *Penicillium* spp.; 65 mL/100 kg seed on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported as proposed.
Tank-mix with Stress Shield at labelled rates on wheat, barley, oat, rye, triticale, millet, pearl millet, proso millet	Supported on wheat, barley and oat.
Seed rot and pre-emergence damping-off caused by seed-borne and soil-borne *Fusarium* spp.; 65 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Post-emergence damping-off caused by soil-borne *Fusarium* spp.; 65 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Seed rot / pre-emergence damping off caused by soil-borne *Pythium* spp.; 65 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Seed rot / pre-emergence damping off caused by *Rhizoctonia solani*; 65 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Seed rot and pre-emergence damping-off caused by seed-borne *Cladosporium* spp. and *Aspergillus* spp.; 65 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Suppression of seed rot and pre-emergence damping-off caused by *Penicillium* spp.; 65 mL/100 kg seed on corn (field, sweet, popcorn)	Supported as proposed.
Root rot caused by seed-borne *Fusarium* spp.; 65 mL/100 kg seed on corn (field, sweet, popcorn)	Not supported. Treatment with PENPROME 177FS resulted in low efficacy against corn root rot caused by seed-borne *Fusarium* spp. (≤50% reduction).
Tank-mix with Trilex FS on corn (field, sweet, popcorn)	Supported as proposed.
Tank-mix with Poncho 600 FS on corn (field, sweet, popcorn)	Supported as proposed.

Proposed claim	Supported / unsupported
Seed rot / pre-emergence damping-off and post-emergence damping-off caused by *Rhizoctonia solani*, *Fusarium* spp., and *Pythium* spp.; 65 mL/100 kg seed on dry shelled peas and beans, including soybean	Supported as proposed.
Early-season root rot and seedling blight caused by *Rhizoctonia solani* and *Fusarium* spp.; 65 mL/100 kg seed on dry shelled peas and beans, including soybean	Supported as proposed.
Seed rot / pre-emergence damping-off caused by seed-borne *Botrytis cinerea*; 65 mL/100 kg seed on dry shelled peas and beans, including soybean	Conditionally supported.
Seedling blight caused by seed-borne *Botrytis cinerea*; 65 mL/100 kg seed on dry shelled peas and beans, including soybean	Supported as proposed.
Seed rot / pre-emergence damping-off of soybean caused by *Phomopsis longicolla*; 65 mL/100 kg seed on dry shelled peas and beans, including soybean	Supported as proposed.
Suppression of seed-borne ascochyta blight in field pea, chickpea, and lentil caused by *Ascochyta* spp.; 65 mL/100 kg seed on dry shelled peas and beans, including soybean	PENPROME 177FS showed inconsistent efficacy against seed-borne *Ascochyta* spp. and the product performance was not assessed under field conditions. Only the following claim is supported: suppression of seed rot / pre-emergence damping-off of chickpea caused by seed-borne *Ascochyta rabiei*; 65 mL/100 kg seed on dry shelled peas and beans, including soybean
Tank-mix with Stress Shield at labelled rates on soybean	Supported as proposed.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Penflufen is a new active ingredient which is concurrently being registered in the United States. The USEPA is in agreement with the specified Canadian MRLs and will be promulgating the same tolerances (40 CFR Part 180).

Currently, there are no Codex MRLs established for penflufen.

Table 1 Differences between MRLs in Canada and in other jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Crop Subgroup 1C – Tuberous and Corm Vegetables Subgroup	0.01	0.01	Not reviewed by Codex
Crop Group 6 – Legume Vegetables (Succulent or Dried)	0.01	0.01	
Crop Group 15 – Cereal Grains	0.01	0.01	
Crop Group 20 – Oilseeds	0.01	0.01	
Eggs; fat, meat and meatbyproducts of cattle, goats, hogs, horses, poultry and sheep; milk	0.01	0.01	

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

1885879 2010, Determination of impurities in penflufen (BYF 14182), DACO: 2.16

1885880 2010, 1st addendum to internal certificate MZ 00216, DACO: 2.13.3 CBI

1885881 2009, BYF 14182, pure substance, melting point, boiling point and thermal stability, DACO: 2.14.13, 2.14.4, 2.14.5

1885882 2009, BYF 14182, pure substance , vapour pressure, DACO: 2.14.9

1885918 2010, An analytical method for the determination of residues of BYF 14182 and its metabolites BYF 14182-3-hydroxy-butyl and BYF 14182-pyrazolyl-AAP in water using LC/MS/MS, DACO: 8.2.2.3

1885919 2009, Analytical method 01147 for the determination of BYF 14182 in drinking and surface water by HPLC-MS/MS, DACO: 8.2.2.3

1885920 2009, Analytical method 01153 for the determination of residues of BYF14182 in Soil by HPLC-MS/MS, DACO: 8.2.2.1

1885921 2008, Analytical procedure for the determination of an impurity, DACO: 2.13.4 CBI

1886034 2009, BYF14182 - Determination of active substance in technical material GC - internal standard, DACO: 2.13.1 CBI

1886035 2009, BYF14182 - Determination of impurities - internal standard, DACO: 2.13.4 CBI

1886036 2009, BYF14182 - Determination of by-products in technical material - internal standard, DACO: 2.13.4 CBI

1886040 2009, Chemical storage stability of BYF 14182 - Amendment No. 1, DACO: 2.14.14

1886046 2009, CSF of penflufen TC - 264-XXXX.0B0, DACO: 2.12.2 CBI

1886047 2008, Determination of impurities, DACO: 2.13.4 CBI

1886050 2009, Determination of the pH-value of BYF 14182, pure substance, DACO: 2.16

1886073 2008, Determination of impurities, DACO: 2.13.4 CBI

1886105 2010, In house validation of the analytical method for the determination of residues of BYF 14182 and its metabolites BYF 14182-3-hydroxy-butyl and BYF 14182-pyrazolyl-AAP in water using LC/MS/MS, DACO: 8.2.2.3

1886111 2010, Independent laboratory validation of method EL-001-W08-01 for the determination of residues of BYF 14182 and its metabolites BYF 14182-3-hydroxy-butyl and BYF14182-pyrazolyl-AAP in water using LC/MS/MS, DACO: 8.2.2.3

1886113 2009, Independent laboratory validation of modification M001 to the analytical method 01035 for the determination of residues of BYF 14182 and its metabolites, BYF14182-3-hydroxy-butyl and BYF14182-pyrazolyl-AAP in soil and sediment by HPLC-MS/MS, DACO: 8.2.2.2

1886121 2009, Material accountability of penflufen (BYF14182), DACO: 2.13.3 CBI

1886122 2009, Material accountability of penflufen (BYF14182) - Chronic tox sample and bridging tox, DACO: 2.13.3 CBI

1886146 2009, Modification M001 to the analytical method 01035 for the determination of residues of BYF14182 and its metabolites, BYF14182-3-hydroxy-butyl and BYF14182-pyrazolyl-AAP in soil and sediment by HPLC-MS/MS, DACO: 8.2.2.2

1886153 2009, Penflufen (BYF 14182) - Technical grade active substance - Description of the manufacturing process of the technical A.S., DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4 CBI

1886154 2009, Penflufen (BYF 14182) - Technical material - Discussion of the formation of impurities, DACO: 2.11.1, 2.11.3, 2.11.4 CBI

1886155 2010, Penflufen (BYF 14182) - Toxicological equivalence assessment of the technical specification with the material tested in toxicity studies, DACO: 2.13.3

1886156 2009, Penflufen (BYF 14182), pure substance: Water solubility at pH 4, pH 7, pH 9 and in distilled water (Flask method), DACO: 2.14.7

1886157 2009, Penflufen (BYF 14182), pure substance: Dissociation constant in water, DACO: 2.14.10, 8.2.3.2

1886158 2009, Penflufen (BYF 14182), pure substance: Partition coefficients 1-octanol / water at pH 4, pH 7 and pH 9 (HPLC method), DACO: 2.14.11

1886165 2009, Penflufen (BYF 14182), technical substance: Melting point, boiling point, thermal stability, DACO: 2.14.13, 2.14.4, 2.14.5

1886166 2009, Penflufen (BYF 14182), technical substance: Oxidizing properties, DACO: 2.16

1886168 2009, Penflufen (BYF 14182), technical substance: Physical characteristics colour, physical state and odour, DACO: 2.14.1, 2.14.2, 2.14.3

1886169 2009, Penflufen (BYF 14182), technical substance: Relative density, DACO: 2.14.6

1886170 2009, Penflufen (BYF 14182), technical substance: The oxidation or reduction properties, DACO: 2.16

1886171 2009, Penflufen (BYF 14182): Calculation of the Henrys law constant, DACO: 2.16

1886172 2009, Penflufen (BYF 14182): Solubility in organic solvents, DACO: 2.14.8

1886173 2009, Penflufen (BYF 14182): Statement on the dielectric breakdown voltage according to OPPTS 830.6321, DACO: 2.16

1886174 2009, Penflufen (BYF 14182): Statement on the miscibility according to OPPTS 830.6319, DACO: 2.16

1886175 2009, Penflufen (BYF 14182): Statement on the viscosity according to OPPTS 830.7100, DACO: 2.16

1886181 2009, Physical characteristics color, physical state and odor of BYF 14182, pure substance, DACO: 2.14.1, 2.14.2, 2.14.3

1886189 2009, Relative density of BYF 14182, pure substance, DACO: 2.14.6

1886191 2009, Spectral data set of BYF 14182 a.i. - Technical batch - Amendment no.1, DACO: 2.13.2, 2.14.12

1886193 2009, Stablility to normal and elevated temperature, metals, and metal ions and corrosion characteristics to platic containers of penflufen (BYF 14182) according to OPPTS 830.6313 and 830.6320, DACO: 2.14.13, 2.14.14

1886194 2009, Statement of product specification form - Penflufen technical fungicide, DACO: 2.12.2 CBI

1886273 2009, Validation of AM007709MP2 and AM007809MP2, DACO: 2.13.4 CBI

1886274 2009, Validation of method for determination of impurities in technical material – external standard, DACO: 2.13.4 CBI

1886275 2009, Validation of method for impurities, DACO: 2.13.4 CBI

1886276 2009, Validation of penflufen (BYF 14182-a.i.) - Determination of active substance in technical material - internal standard - 1st amendment, DACO: 2.13.1 CBI

1954091 2010, Tier 2 summary of the identity of the active substance, DACO: 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9

1972382 2010, BCS response to questions received from the PMRA (September 7, 2010) regarding the product chemistry for Penflufen TC (Sub. No. 2010-1288), DACO: 2.11, 2.13.1, 2.13.3 CBI

1984248 2010, Penflufen TC, Response to chemistry clarifications, DACO: 8.2.2

1984250 2007, Analytical method 01035 for the determination of residues of BYF 14182 and BYF14182-3-hydroxybutyl in soil by HPLC-MS/MS, DACO: 8.2.2.1

1987803 2010, Penflufen TC, DACO: 2.13.2 CBI

2003833 2010, Spectral data (NMR and MS) for specified impurities in PENFLUFEN (BYF14182) technical material, DACO: 2.13.2 CBI

2069140 2011, BCS response to questions received from the PMRA (June 14, 2011) regarding the product chemistry for Penflufen TC, DACO: 2.11.1, 2.11.3, 2.11.4, 2.13.3, 2.13.4, 2.14.1, 2.14.2 CBI

2069141 2011, Penflufen (BYF 14182) Technical Grade Active Substance, Description of the manufacturing process of the technical A.S., DACO: 2.11.1, 2.11.3, 2.11.4 CBI

2069142 2009, Physical characteristics (colour and physical state) of five batches of Penflufen, technical substance, DACO: 2.14.1, 2.14.2

2069143 2010, Validation of AM007709MP2 and AM007809MP2, Amendment No.1, DACO: 2.13.4 CBI

2.0 Human and Animal Health

1039215 1989, Exposure of seed treatment workers to isofenphos during application of Oftanol containing seed coating to canola seed, DACO: 5.4

1039216 1990, Exposure of workers to isofenphos during planting of Oftanol treated canola seed, DACO: 5.6

1335563 2006, Gaucho 480 SC – Worker exposure during on-farm and commercial seed treatment of cereals, DACO: 5.4

1372835 2006, Determination of dermal and inhalation exposure of workers during on-farm seed piece treatment of potatoes, DACO: 5.4

1525896 2001, Determination of exposure to pencycuron during loading and application of Moncereen–Droogontsmetter (Moncereen DS 12.5) in potato fields, DACO: 5.6

1885209 2010, Observational study to determine dermal and inhalation exposure to workers in commercial seed treatment facilities: mixing/treating with a liquid pesticide product and equipment clean-outs, DACO: 5.4

1885217 2009, BYF 14182 (FS 240): *In vivo* dermal absorption study in male rat, DACO: 5.8

1885273 2009, BYF 14182 FS 240 (red) - acute toxicity in the rat after oral administration, DACO: 4.6.1

1885274 2009, BYF 14182 FS 240 (red) - acute toxicity in the rat after dermal administration, DACO: 4.6.2

1885275 2009, BYF 14182 FS 240 (red) - Acute inhalation toxicity in rats, DACO: 4.6.3

1885276 2009, BYF 14182 FS 240 (red) - Acute skin irritation/corrosion on rabbits, DACO: 4.6.5

1885279 2009, BYF 14182 FS 240 (red) - Acute eye irritation on rabbits, DACO: 4.6.4

1885280 2009, BYF 14182 FS 240 (red) - Evaluation of potential skin sensitization in the local lymph node assay in the mouse, DACO: 4.6.6

1885322 2010, BYF 14182 + prothioconazole FS 100+18 g/L - Acute toxicity in the rat after oral administration, DACO: 4.6.1

1885323 2010, BYF 14182 + prothioconazole FS 100+18 g/L - Acute toxicity in the rat after dermal application, DACO: 4.6.2

1885324 2010, BYF 14182 + prothioconazole FS 100+18g/L - Activity ID TXELP112 - Acute inhalation toxicity in rats, DACO: 4.6.3

1885325 2010, BYF 14182 + prothioconazole FS 100+18 g/L - Acute skin irritation/corrosion on rabbits, DACO: 4.6.5

1885326 2010, BYF 14182 + prothioconazole FS 100+18 g/L - Acute eye irritation on rabbits, DACO: 4.6.4

1885328 2010, BYF 14182 + prothioconazole FS 100+18 g/L - Evaluation of potential skin sensitization in the local lymph node assay in the mouse, DACO: 4.6.6

1885681 2010, BYF 14182 + clothianidin FS 66.5+207 g/L - Acute toxicity in the rat after oral administration, DACO: 4.6.1

1885682 2010, BYF 14182 + clothianidin FS 66.5+207 g/L - Acute toxicity in the rat after dermal application, DACO: 4.6.2

1885683 2010, BYF 14182 + clothianidin FS 66.5+207 g/L - Activity ID TXELP058 - Acute inhalation toxicity in rats, DACO: 4.6.3

1885684 2010, BYF 14182 + clothianidin FS 66.5+207 g/L - Acute skin irritation/corrosion on rabbits, DACO: 4.6.5

1885685 2010, BYF 14182 + clothianidin FS 66.5+207 g/L - Acute eye irritation on rabbits, DACO: 4.6.4

1885686 2010, BYF 14182 + clothianidin FS 66.5+207 g/L - Evaluation of potential skin sensitization in the local lymph node assay in the mouse, DACO: 4.6.6

1885711 2009, BYF 14182 + clothianidin + metalaxyl + trifloxystrobin FS 10,7 +290 +7,15+ 7,15 acute toxicity in the rat after oral administration, DACO: 4.6.1

1885712 2009, BYF 14182 + clothianindin + metalaxyl + trifloxstrobin FS 10,7 +290 +7,15 +7,15 acute toxicity in the rat after dermal application, DACO: 4.6.2

1885713 2009, BYF 14182 + clothianidin + metalaxyl + trifloxystrobin FS 10.7 +290 +7.15 +7.15 - Activity ID TXELP103 - Acute inhalation toxicity in rats, DACO: 4.6.3

1885714 2009, BYF 14182 + clothianidin + metalaxyl + trifloxystrobin FS 10,7 +290 +7,15 +7,15 - Acute skin irritation/corrosion on rabbits, DACO: 4.6.5

1885715 2010, BYF 14182 + clothianidin + metalaxyl + trifloxystrobin FS 10,7 +290 +7,15 +7,15 - Acute eye irritation on rabbits, DACO: 4.6.4

1885716 2009, BYF 14182 + clothianidin + metalaxyl + trofloxystrobin FS 10.7 +290 +7.15 +7.15 g/L - Evaluation of potential skin sensitization in the local lymph node assay in the mouse, DACO: 4.6.6

1885743 2009, BYF 14182 + prothioconazole + metalaxyl FS 38.4 +76.8 +61.4 - Acute toxicity in the rat after oral administration, DACO: 4.6.1

1885744 2009, BYF 14182 + prothioconazole + metalaxyl FS 38.4 +76.8 +61.4 - Acute toxicity in the rat after dermal application, DACO: 4.6.2

1885745 2009, BYF 14182 + prothioconazole + metalaxyl FS 38.4 +76.8 +61.4 - Activity ID TXELP089 - Acute inhalation toxicity in rats, DACO: 4.6.3

1885746 2009, BYF 14182 + prothioconazole + metalaxyl FS 38.4 +76.8 +61.4 - Acute skin irritation/corrosion on rabbits, DACO: 4.6.5

1885748 2009, BYF 14182 + prothioconazole + metalaxyl FS 38.4 +76.8 +61.4 - Acute eye irritation on rabbits, DACO: 4.6.4

1885749 2009, BYF 14182 + prothioconazole + metalaxyl FS 38.4 +76.8 +61.4 - Evaluation of potential skin sensitization in the local lymph node assay in the mouse, DACO: 4.6.6

1885751 2010, Determination of the total radioactive residue (TRR) of [14C] prothioconazole in alfalfa following seed treatment, DACO: 7.4.1, 7.4.2, 7.4.6

1885808 2009, BYF 14182 & trifloxystrobin FS 154 + 154 (blue) - Acute toxicity in the rat after oral administration, DACO: 4.6.1

1885810 2009, BYF 14182 & trifloxystrobin FS 154 + 154 (blue) - Acute toxicity in the rat after dermal application, DACO: 4.6.2

1885813 2009, BYF 14182 & trifloxystrobin FS 154 + 154 (blue) - Acute inhalation toxicity in rats, DACO: 4.6.3

1885816 2009, BYF 14182 & trifloxystrobin FS 154 + 154 (blue) - Acute skin irritation/ corrosion on rabbits, DACO: 4.6.5

1885818 2009, BYF 14182 & trifloxystrobin FS 154 + 154 (blue) - Acute eye irritation on rabbits, DACO: 4.6.4

1885820 2009, BYF 14182 & trifloxystrobin FS 154 + 154 (blue) - Evaluation of potential skin sensitization in the local lymph node assay in the mouse, DACO: 4.6.6

1885878 2009, 1. Analytical method no. 01057 for the determination of residues in/on plant material by HPLC-MS/MS of BYF 14182 (AE 1698405) and its metabolites as listed below : BYF 14182-3-hydroxy-butyl (BCS-AA-10006), the conjugates of this metabolite (BYF 14182-3-hydroxy-butyl-maonyl-glucoside and BYF 14182-3-hydroxy-butyl-glucoside), BYF 14182-homoglutathione (BCS-AA10790), BYF 14182-pyrazole-4-carboxamide (BCS-AA10791), BYF 14182-bis-desmthyl-3-carboxylic acid (BCS-CM41431), DACO: 7.2.1, 7.2.4

1885887 2009, [Phenyl-UL-13C6/14C]BYF 14182 - Metabolism in organs and tissues of male and female rats (3 time-points), DACO: 4.5.9

1885890 2009, [Phenyl-UL-13C6/14C]BYF 14182: Absorption, distribution, excretion and metabolism in the rat, DACO: 4.5.9

1885897 2009, [Pyrazole-3-14C]BCS-AA10006 (BYF 14182-3-hydroxy-butyl) - Absorption, distribution, excretion and metabolism in the rat, DACO: 4.5.9

1885901 2009, [Pyrazole-3-14C]BYF 14182: Absorption, distribution, excretion and metabolism in the rat, DACO: 4.5.9

1885904 2009, A subacute dermal toxicity study in rats with BYF 14182, DACO: 4.3.5

1885905 2009, A subchronic neurotoxicity screening study with technical grade BYF 14182 in Wistar rats, DACO: 4.5.13

1885917 2009, An acute oral neurotoxicity screening study with technical grade BYF 14182 in wistar rats, DACO: 4.5.12

1885930 2009, Assessment and applicability of the multi-residue DFG Method S19 for the determination of residues of BYF 14182 and metabolite BCS-AA10006, DACO: 7.2.1, 7.2.4

1885932 2010, Bayer method EL-002-P09-02 - An analytical method for the determination of residues of BYF 14182 and metabolites in crop matrices using LC/MS/MS, DACO: 7.2.1, 7.2.4

1885933 2010, Bayer method EL-002-P09-03 - An analytical method for the determination of residues of BYF 14182 and metabolites in crop matrices using LC/MS/MS, DACO: 7.2.1, 7.2.4

1885937 2010, BFY 14182 240FS red - Magnitude of residues in/on corn (5×), DACO: 7.4.5

1885938 2010, BFY 14182 240FS red - Magnitude of residues in/on soybean (1×), DACO: IIA 6.3.5

1885939 2010, BFY 14182 240FS red - Magnitude of residues in/on soybean (5×), DACO: 7.4.5

1885941 2009, BYF 14182 (project: BYF 14182) - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman) - 1st amendment to report no. AT03941 of July 12, 2007 (study no. T4077325), DACO: 4.2.6

1885943 2009, BYF 14182 - 90-day toxicity study in the mouse by dietary administration, DACO: 4.3.1

1885944 2009, BYF 14182 - 90-day toxicity study in the rat by dietary administration, DACO: 4.3.1

1885946 2009, BYF 14182 - 90-day toxicity study in the rat by dietary administration - complementary study, DACO: 4.3.1

1885947 2009, BYF 14182 - Activity ID TXELP010 - Acute inhalation toxicity in rats, DACO: 4.2.3

1885948 2009, BYF 14182 - Acute eye irritation on rabbits, DACO: 4.2.4

1885949 2009, BYF 14182 - Acute skin irritation/corrosion on rabbits, DACO: 4.2.5

1885950 2009, BYF 14182 - Acute toxicity in the rat after dermal application, DACO: 4.2.2

1885952 2009, BYF 14182 - Acute toxicity in the rat after oral administration, DACO: 4.2.1

1885953 2009, BYF 14182 - Chronic toxicity study in the dog by dietary administration, DACO: 4.3.2

1885954 2009, BYF 14182 - Developmental toxicity study in the rabbit by gavage, DACO: 4.5.3

1885956 2009, BYF 14182 - Developmental toxicity study in the rat by gavage, DACO: 4.5.2

1885958 2009, BYF 14182 - Exploratory 28-day toxicity study in the rat by dietary administration, DACO: 4.3.3

1885959 2009, BYF 14182 - *In vitro* chromosome aberration test with chinese hamster V79 cells, DACO: 4.5.6

1885960 2009, BYF 14182 - Micronucleus-test on the male mouse, DACO: 4.5.7

1885961 2009, BYF 14182 - Preliminary 28-day toxicity study in the dog by dietary administration, DACO: 4.3.3

1885964 2009, BYF 14182 - Preliminary 28-day toxicity study in the mouse by dietary administration, DACO: 4.3.3

1885966 2009, BYF 14182 - Salmonella/microsome test - Plate incorporation and preincubation method, DACO: 4.5.4

1885969 2009, BYF 14182 - Subacute oral immunotoxicity study in Wistar rats (4 weeks administration by diet), DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8

1885975 2009, BYF 14182 - V79/HPRT test *in vitro* for the detection of induced forward mutations, DACO: 4.5.5

1885977 2010, BYF 14182 240 FS red - Magnitude of residues in/on wheat (5×), DACO: 7.4.5

1885997 2010, BYF 14182 FS240 (red) - Magnitude of the residue in/on field corn and sweet corn (CG 15 and 16), DACO: 7.4.1, 7.4.2, 7.4.6

1886004 2010, BYF 14182 FS240 (red) - Magnitude of the residue in/on wheat, DACO: 7.4.1, 7.4.2, 7.4.6

1886005 2010, BYF 14182 FS240 - Magnitude of the residue in field rotational crops (limited rotational crops - wheat, mustard greens, turnips), DACO: 7.4.4

1886007 2010, BYF 14182 FS240 - Magnitude of the residue in/on potato processed commodities, DACO: 7.4.5

1886012 2010, BYF 14182 FS240 - Magnitude of the residue in/on potatoes, DACO: 7.4.1

1886018 2009, BYF 14182-3-hydroxy-butyl (project: BYF 14182) - *in vitro* chromosome aberration test with chinese hamster V79 cells, DACO: 4.8

1886019 2009, BYF 14182-3-hydroxy-butyl (project: BYF 14182) - Salmonella/microsome test - Plate incorporation and preincubation method, DACO: 4.8

1886020 2009, BYF 14182-3-hydroxy-butyl (project: BYF 14182) - V79/HPRT-test *in vitro* for the detection of induced forward mutations, DACO: 4.8

1886024 2009, BYF 14182-3-pyrazolyl-AAP (project: BYF 14182) - V79/HPRT-test *in vitro* for the detection of induced forward mutations, DACO: 4.8

1886025 2009, BYF 14182-pyrazolyl-AAP (project: BYF 14182) - *in vitro* chromosome aberration test with chinese hamster V79 cells, DACO: 4.8

1886026 2009, BYF 14182-pyrazolyl-AAP - (Project: BYF 14182) - Salmonella/microsome test plate incorporation and preincubation method, DACO: 4.8

1886029 2009, BYF 14182: 90-day toxicity study in the dog by dietary administration, DACO: 4.3.2

1886037 2010, BYF14182 240FS red - Magnitude of residues in/on barley, DACO: 7.4.1, 7.4.2, 7.4.6

1886039 2010, Carcinogenicity study of BYF 14182 in the C57BL/6J mouse by dietary administration, DACO: 4.4.3

1886044 2010, Chronic toxicity and carcinogenicity study of BYF 14182 in the wistar rat by dietary administration, DACO: 4.4.2, 4.4.4

1886065 2009, Determination of the total radioactive residue (TRR) of [pyrazole-3-14C] BYF14182 in edible podded legumes following seed treatment, DACO: 6.3

1886066 2010, Determination of the total radioactive residue of [pyrazole-3-14C] BYF14182 in alfalfa following treatment, DACO: 6.3

1886067 2008, Determination of the total radioactive residue of [pyrazole-3-14C] BYF14182 in canola following seed treatment, DACO: 6.3

1886068 2009, Determination of the total radioactive residue of [pyrazole-3-14C] BYF14182 in corn following seed treatment - Amended, DACO: 6.3

1886069 2010, Determination of the total radioactive residue of [pyrazole-3-14C] BYF14182 in cotton following seed treatment, DACO: 6.3

1886070 2008, Determination of the total radioactive residue of [pyrazole-3-14C] BYF14182 in peas (crop group 6B) following seed treatment, DACO: 6.3

1886071 2008, Determination of the total radioactive residue of [pyrazole-3-14C] BYF14182 in sunflower following treatment, DACO: 6.3

1886072 2009, Determination of TRR after application of [phenyl-UL-13C6/14C] and [pyrazole-3-14C] in confined rotational crops, DACO: 7.4.4

1886102 2009, Extraction efficiency testing of the residue analytical method 01057 for the determination of BYF 14182 residues in plant matrices using aged radioactive residues, DACO: 7.2.1, 7.2.4

1886103 2010, FDA PAM Multiresidue method (MRM) testing for penflufen and four metabolites, DACO: 7.2.1, 7.2.4

1886104 2009, Gene mutation assay in chinese hamster v79 cells *in vitro* (V79 / HPRT) with BYF 14182, DACO: 4.5.5

1886106 2009, *In vitro* chromosome aberration test in chinese hamster v79 cells with BYF 14182, DACO: 4.5.6

1886107 2010, Independent laboratory validation of Bayer method EL-002-P09-02 An analytical method for the determination of residues of BYF 14182 and metabolites in crop matrices using LC/MS/MS - Final Report, DACO: 7.2.1, 7.2.4

1886110 2009, Independent laboratory validation of BCS analytical method no. 01057 for the determination of residues of BYF 14182 and metabolite BCS-AA10006 in plant materials, using LC/MS/MS, DACO: 7.2.1, 7.2.4

1886123 2009, Metabolism of (pyrazole-3-14C]BYF 14182 in the laying hen, DACO: 6.2

1886124 2009, Metabolism of [phenyl-UL-13C6/14C)BYF 14182 in soybeans after seed dressing, DACO: 6.3

1886125 2009, Metabolism of [phenyl-UL-13C6/14C]BYF 14182 in confined rotational crops, DACO: 7.4.4

1886126 2009, Metabolism of [phenyl-UL-13C6/14C]BYF 14182 in paddy rice, DACO: 6.3

1886128 2009, Metabolism of [phenyl-UL-13C6/14C]BYF 14182 in potatoes, DACO: 6.3

1886129 2009, Metabolism of [phenyl-UL-13C6/14C]BYF 14182 in spring wheat after seed dressing, DACO: 6.3

1886130 2009, Metabolism of [phenyl-UL-13C6/14C]BYF 14182 in the lactating goat, DACO: 6.2

1886131 2009, Metabolism of [phenyl-UL-13C6/14C]BYF 14182 in the laying hen, DACO: 6.2

1886132 2009, Metabolism of [pyrazole-3-14C]BYF 14182 in confined rotational crops, DACO: 7.4.4

1886133 2009, Metabolism of [pyrazole-3-14C]BYF 14182 in paddy rice, DACO: 6.3

1886134 2009, Metabolism of [pyrazole-3-14C]BYF 14182 in potatoes, DACO: 6.3

1886135 2009, Metabolism of [pyrazole-3-14C]BYF 14182 in soybeans after seed dressing, DACO: 6.3

1886136 2009, Metabolism of [pyrazole-3-14C]BYF 14182 in spring wheat after seed dressing, DACO: 6.3

1886137 2009, Metabolism of [pyrazole-3-14C]BYF 14182 in the lactating goat, DACO: 6.2

1886180 2009, Phase report: 9 months storage stability of study 08-16 - Storage stability of residues of BYF 14182 and its metabolites (BCS-AA10006, BCS-AA10790, BCS-AA10791 and BCS-CM41431) in plants during deep freeze storage for up to 24 months, DACO: 7.3

1886187 2009, Quantitative whole body autoradiography of [phenyl-UL-$^{13}C_6/^{14}C$]BYF 14182 in male and female rats: distribution of radioactivity and elimination from blood, organs and tissues after single oral administration including determination of radioactivity in the excreta and exhaled $^{14}CO_2$, DACO: 4.5.9

1886188 2009, Quantitative whole body autoradiography of [pyrazole-3-^{14}C]BYF 14182 in male and female rats: distribution of radioactivity and elimination from blood, organs and tissues after single oral administration including determination of radioactivity in the excreta and exhaled $^{14}CO_2$, DACO: 4.5.9

1886190 2009, *Salmonella typhimurium* reverse mutation assay with BYF 14182, DACO: 4.5.4

1886196 2009, Storage stability of BYF 14182 residues in plant matrices, DACO: 7.3

1886198 2009, Technical grade BYF 14182: A two-generation reproductive toxicity study in the wistar rat, DACO: 4.5.1

1886277 2010, Validation of the residue analytical method 01192 for the determination of BYF 14182 and its metabolite BYF 14182-3,4-dihydroxy in animal tissues (bovine liver, kidney, muscle, fat, milk and poultry liver, muscle, fat, and eggs) by HPLC-MS/MS, DACO: 7.2.1, 7.2.4

1886279 2010, Waiver of the requirement for a livestock feeding study for penflufen, DACO: 7.5,7.6

1930403 2010, Bayer Response to PMRA e-mail regarding PMRAs completeness check of submissions 2010-1288 and 2010-1276 (Penflufen TC and Penflufen TC-MRL submission), DACO: 4.4.4, 4.5.12, 4.5.13

1930404 1993, Historical control and method validation studies in rats for the acute and subchronic neurotoxicity screening battery, DACO: 4.5.12, 4.5.13

1930406 2004, Verification of personnel training to perform a functional observational battery with rats, DACO: 4.5.12, 4.5.13

1930407 2002, Motor activity assessment (Lab Room 304) - Historical control and method validation study using triadimefon and chlorpromazine in wistar rats, DACO: 4.5.12, 4.5.13

1930409 2009, An experimental functional observational battery validation study with carbaryl in wistar rats, DACO: 4.5.12, 4.5.13

1965959 2010, Laboratory dust-off study of different cereal, pulse, oilseed and corn seeds treated with penflufen based seed treatment formulations – addendum 1, DACO: 5.4

1965962 2008, Determination of operator exposure to imidacloprid during loading/sowing of Gaucho treated maize seeds under realistic field conditions in Germany and Italy, DACO: 5.6

1967877 2005, BYF 14182: Summary/conclusions of range-finding study for developmental toxicity in the rabbit by gavage (Study No. SA 04193), DACO: 4.5.3

1967878 2005, BYF 14182: Summary/conclusions of range-finding study with fetal evaluation for developmental toxicity in the rat by gavage (Study No. SA 04192), DACO: 4.5.2

1967879 2009, Technical Grade BYF 14182: A dose range-finding repoductive toxicity study in the wistar rat, DACO: 4.5.1

2026516 2011, Bayer response to EPA e-mail regarding EPAs request for penflufen historical control data from testing facility, DACO: 4.8

2026877 2010, Validation of the residue analytical method 01192 for the determination of BYF 14182 and its metabolite BYF 14182-3,4-dihydroxy in animal tissues (bovine liver, kidney, muscle, fat, milk and poultry liver, muscle, fat, and eggs) by HPLC-MS/MS, DACO: 7.2.1

2026878 2010, Radiovalidation of the residue analytical method 01192 for the determination of BYF 14182 and its metabolite BYF 14182-3,4-dihydroxy in animal tissues using aged radioactive residues in liver, DACO: 7.2.1

2026879 2010, Penflufen - Magnitude of the residue in dairy cows, DACO: 7.5.1

2026886 2010, An analytical method for the determination of residues of BYF 14182and its metabolite BYF 14182-3,4-dihydroxy in animal tissues using LC/MS/MS, DACO: 7.2.1

2040191 2006, Validation of the Magnusson-Kligman maximization test method performed in Guinea pigs of the strain Crl:HA with alpha hexyl cinnamic aldehyde, DACO: 4.2.6

2068943 2011, Storage stability of residues of BYF 14182 and its metabolites (BCS-AA10006, BCS-AA10790, BCS-AA10791 and BCS-CM41431) in plants during deep freeze storage for up to 24 months., DACO: 7.3

3.0 Environment

1885883 2010, [Phenyl-UL-13C6/14C] and [pyrazole-3-14C]BYF 14182 - Photolysis in natural water, DACO: 8.2.3.3.2

1885884 2009, [Phenyl-UL-13C6/14C] and [pyrazole-3-14C]BYF 14182: Hydrolytic degradation, DACO: 8.2.3.2

1885885 2009, [Phenyl-UL-13C6/14C] BYF14182: Adsorption/desorption on five soils, DACO: 8.2.4.2

1885886 2009, [Phenyl-UL-$^{13}C_6$/^{14}C]-BYF 14182: Bioconcentration and biotransformation in fish (*Lepomis macrochirus)*, DACO 9.5.6

1885889 2009, [Phenyl-UL-13C6/14C]BYF 14182 and [pyrazole-3-14C]BYF 14182: Phototransformation in aqueous buffer, DACO: 8.2.3.3.2

1885891 2009, [Phenyl-UL-14C] and [pyrazole-3-14C] BYF 14182: Aerobic soil metabolism in two US soils, DACO: 8.2.3.4.2

1885892 2008, [phenyl-UL-14C] and [pyrazole-3-14C]BYF 14182: Anaerobic aquatic metabolism, DACO: 8.2.3.5.5, 8.2.3.5.6

1885893 2009, [Phenyl-UL-14C] BYF14182: Aerobic soil metabolism/degradation and time-dependent sorption in four soils, DACO: 8.2.3.4.2

1885894 2009, [Pyrazole-3-14C] and [phenyl-UL-14C]BYF14182: Aerobic aquatic degradation, DACO: 8.2.3.6

1885895 2008, [Pyrazole-3-14C] and [phenyl-UL-14C]BYF14182: Anaerobic soil metabolism, DACO: 8.2.3.4.4

1885898 2009, [Pyrazole-3-14C]BCS-AF73126 (BYF 14182-pyrazolyl-AAP): Adsorption/desorption on five soils, DACO: 8.2.4.2

1885899 2009, [Pyrazole-3-14C]BCS-AF73126 (BYF 14182-pyrazolyl-AAP): Degradation and time-dependent sorption in soils, DACO: 8.2.3.4.2

1885903 2009, [Pyrazole-3-14C]BYF14182-3-hydroxy-butyl (BCS-AA10006): Adsorption/desorption in five different soils, DACO: 8.2.4.2

1885906 2009, Acute toxicity of BYF 14182 (tech.) to fish (*Cyprinus carpio*) under static conditions, DACO: 9.5.2.2, 9.5.2.3

1885907 2009, Acute toxicity of BYF 14182 technical to bluegill (*Lepomis macrochirus*) under static conditions, DACO: 9.5.2.2, 9.5.2.3

1885908 2009, Acute toxicity of BYF 14182 technical to crayfish under static conditions, DACO: 9.3.4

1885909 2008, Acute toxicity of BYF 14182 technical to *Daphnia magna* under static conditions, DACO: 9.3.2

1885910 2009, Acute toxicity of BYF 14182 technical to the fathead minnow (*Pimephales promelas*) under static conditions, DACO: 9.5.2.2, 9.5.2.3

1885911 2009, Acute toxicity of BYF 14182 technical to the rainbow trout (*Oncorhynchus mykiss*) under static conditions, DACO: 9.5.2.1, 9.5.2.3

1885912 2009, Acute toxicity of BYF 14182 technical to the sheepshead minnow (*Cyprinodon variegatus*) under static conditions, DACO: 9.4.2, 9.4.3, 9.4.4

1885913 2009, Acute toxicity of BYF 14182-3-hydroxy-butyl to *Daphnia magna* under static conditions, DACO: 9.3.2

1885914 2009, Acute toxicity of BYF14182-pyrazolyl-AAP (tech.) to the waterflea *Daphnia magna* in a static laboratory test system, DACO: 9.3.2

1885915 2009, Acute toxicity of penflufen-3-hydroxy-butyl to fish (*Cyprinus carpio*) under static conditions, DACO: 9.5.2.3, 9.5.2.4

1885916 2009, Acute toxicity of penflufen-pyrazolyl-AAP to fish (*Cyprinus carpio*) under static conditions, DACO: 9.5.2.3, 9.5.2.4

1885942 2009, BYF 14182 (tech.): Acute toxicity to earthworms (*Eisenia fetida*) tested in artificial soil with 5 percent peat, DACO: 9.2.3.1

1885991 2009, BYF 14182 FS 240 g/L - Effects on eleven species of non-target terrestrial plants: seedling emergence and growth test (Tier 1), DACO: 9.8.4

1885992 2009, BYF 14182 FS 240 g/L - Effects on eleven species of non-target terrestrial plants: vegetative vigour test (Tier 1), DACO: 9.8.4

1885995 2009, BYF 14182 FS 240: Influence on mortality and reproduction on the soil mite species *Hypoaspis aculeifer* tested in artificial soil with 5 percent peat, DACO: 9.3.4, 9.6.6, 9.9

1886021 2009, BYF 14182-3-hydroxy-butyl: Effects on survival, growth and reproduction on the earthworm *Eisenia fetida* tested in artificial soil with 5 percent peat, DACO: 9.2.3.1

1886023 2009, BYF 14182-3-hydroxy-butyl: Influence on mortality and reproduction on the soil mite species *Hypoaspis aculeifer* tested in artificial soil with 5 percent peat, DACO: 9.3.4, 9.6.6, 9.9

1886027 2009, BYF 14182-pyrazolyl-AAP: Influence on mortality and reproduction on the soil mite species *Hypoaspis aculeifer* tested in artificial soil with 5 percent peat, DACO: 9.3.4, 9.6.6, 9.9

1886028 2009, BYF 14182-pyrazolyl-AAP: Sublethal toxicity to the earthworm *Eisenia fetida* in artificial soil with 5 percent peat, DACO: 9.2.3.1

1886030 2009, BYF 14182: A 96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*), DACO: 9.4.2, 9.4.3, 9.4.4

1886031 2008, BYF 14182: A 96-hour static acute toxicity test with the saltwater mysid (*Americamysis bahia*), DACO: 9.4.2, 9.4.3, 9.4.4

1886033 2009, BYF 14812 FS 240: Effects on survival, growth and reproduction on the earthworm *Eisenia fetida* tested in artificial soil with 5 percent peat, DACO: 9.2.3.1

1886045 2009, Chronic toxicity of BYF 14182 technical to the *Daphnia magna* under static renewal conditions, DACO: 9.3.3

1886096 2009, Early life stage toxicity of BYF 14182 technical to the fathead minnow (*Pimephales promelas*) under flow-through conditions, DACO: 9.5.3.1

1886098 2009, Effects of BYF 14182 (acute contact and oral) on honey bees (*Apis mellifera* L.) in the laboratory, DACO: 9.2.4.2

1886186 2009, *Pseudokirchneriella subcapitata* growth inhibition test with BYF 14182-pyrazolyl-AAP, DACO: 9.8.2, 9.8.3

1886192 2009, Spiked whole sediment 10-day toxicity test of BYF 14182 technical to *Chironomus dilutus* (formerly known as *Chironomus tentans*), DACO: 9.9

1886197 2009, Supplement to Report MEF-09/466 Kinetic evaluation of the aerobic metabolism of BYF 14182-pyrazolyl-AAP in four soils for the determination of modelling endpoints BYF 14182-Pyrazolyl-AAP (BCS-AF73126), DACO: 8.2.3.4.2

1886211 2010, Terrestrial field dissipation of BYF 14182 in Idaho soil, 2007, DACO 8.3.2.2

1886212 2010, Terrestrial field dissipation of BYF 14182 in Ontario, Canada soil, 2007, DACO 8.3.2.1

1886218 2010, Terrestrial field dissipation of BYF 14182 in Prince Edward Island, Canada soil, 2007, DACO 8.3.2.1

1886221 2010, Terrestrial field dissipation of BYF 14182 in Saskatchewan, Canada soil, 2007, DACO 8.3.2.1

1886257 2010, Toxicity of BYF 14182 technical during an actue oral LD50 with the canary (*Serinus canaria*), DACO: 9.6.2.1,9.6.2.2,9.6.2.3

1886258 2009, Toxicity of BYF 14182 technical during an acute dietary LC50 with the mallard duck (*Anas platyrhynchos*), DACO: 9.6.2.6

1886260 2009, Toxicity of BYF 14182 technical during an acute dietary LC50 with the Northern bobwhite quail (*Colinus virginianus*), DACO: 9.6.2.4, 9.6.2.5

1886261 2009, Toxicity of BYF 14182 technical during an acute oral LD50 with the Northern bobwhite quail (*Colinus virginianus*), DACO: 9.6.2.1, 9.6.2.2, 9.6.2.3

1886262 2009, Toxicity of BYF 14182 technical on reproduction to the northern bobwhite quail (*Colinus virginianus*), DACO: 9.6.3.1, 9.6.3.2, 9.6.3.3

1886263 2009, Toxicity of BYF 14182 technical on reproduction to the mallard duck (*Anas platyrhynchos*), DACO: 9.6.3.1, 9.6.3.2, 9.6.3.3

1886264 2009, Toxicity of BYF 14182 technical to duckweed (*Lemna gibba* G3) under static-renewal conditions, DACO: 9.8.5

1886265 2007, Toxicity of BYF 14182 technical to the green alga *Pseudokirchneriella subcapitata*, DACO: 9.8.2, 9.8.3

1886266 2009, Toxicity of BYF 14182-3-hydroxy-butyl to the green alga *Pseudokirchneriella subcapitata*, DACO: 9.8.2, 9.8.3

1886267 2009, Toxicity to the parasitoid wasp *Aphidius rhopalosiphi* (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) in the laboratory BYF 14182 FS 240 G, DACO: 9.2.6

1886269 2009, Toxicity to the predatory mite *Typhlodromus pyri* Scheuten (Acari, Phytoseiidae) in the laboratory BYF 14182 FS 240 G, DACO: 9.2.5

1945520 2010, Determination of the storage stability of BYF14182 and its metabolites BYF14182-3-hydroxybutyl (BCS-AA10006) and BYF14182 pyrazolyl-AAP (AE 2300037) in soil, DACO: 8.6

4.0 Value

1885194 2010, PEN 240 FS flowable fungicide, DACO: 5.2, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.2.3.4, 10.3.1, 10.3.2, 10.4, 10.5.1, 10.5.2, 10.5.4

1885202 2010, Penflufen fungicide and associated co-formulations for control of seed and soil borne diseases of potato, DACO: 5.2, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.2.3.4, 10.3.1, 10.3.2, 10.4, 10.5.1, 10.5.2, 10.5.4

1885708 2010, PENCLOTRIME 310.68FS fungicide and insecticide seed treatment, DACO: 5.2, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.2.3.4, 10.3.1, 10.3.2, 10.4, 10.5.1, 10.5.2, 10.5.4

1885739 2010, PENPROME 177FS seed treatment fungicide, DACO: 5.2, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.2.3.4, 10.3.1, 10.3.2, 10.4, 10.5.1, 10.5.2, 10.5.4

1885801 2010, Pentri 308FS seed treatment fungicide, DACO: 5.2, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.2.3.4, 10.3.1, 10.3.2, 10.4, 10.5.1, 10.5.2, 10.5.4

1935301 2010, Bayer CropScience response to deficiencies identified by the PMRA for the value data packages submitted in support of PEN 240FS, PENRED 240FS, PENCLO 273.5FS, PENCLOTRIME 310.68FS, PENPROME 177FS and PENTRI 308FS, DACO: 10.2.3.3(D)