Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Penflufen in the Product EverGol Prime Seed Treatment

APVMA Product Number 64744

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This publication is available from the APVMA website: www.apvma.gov.au.

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing, Office of Chemical Safety (OCS), Department of Sustainability, Environment, Water, Population and Communities (DSEWPaC), and State Departments of Primary Industries.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents.

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined in the APVMA's publications *Ag MORAG: Manual of Requirements and Guidelines* and *Vet MORAG: Manual of Requirements and Guidelines*.

This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop safety.

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **EverGol Prime Seed Treatment** should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **28 November 2012** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing *via* email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- Contact name
- Company or group name (if relevant)
- Email or postal address (if available)
- The date you made the submission.

All personal information, and confidential information judged by the APVMA to be ***confidential commercial information (CCI)***[1] contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the **grounds for registration** should be addressed in writing to:

Contact Officer Pesticides Program
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604
Phone: 02 6210 4748
Fax: 02 6210 4776
Email: pesticides@apvma.gov.au

[1] A full definition of "confidential commercial information" is contained in the Agvet Code.

Further information

Further information can be obtained *via* the contact details provided above.

Copies of full technical evaluation reports covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on public release summaries can be found on the APVMA website: www.apvma.gov.au

1 INTRODUCTION

1.1 Purpose of application

Bayer CropScience Pty Ltd has applied to the APVMA for approval of the new product EverGol Prime Seed Treatment (formerly PENRED 240 FS) containing the new active constituent penflufen (240 g/L) as a flowable concentrate for seed treatment. The application was jointly reviewed with regulatory authorities in Canada and the United States.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of EverGol Prime Seed Treatment, and approval of the new active constituent penflufen.

1.2 Function of active constituent

Penflufen is an alkylamide fungicide belonging to the subclass pyrazole-carboxamide. Penflufen is xylem-mobile and has systemic properties that affects target pests by inhibition of succinate dehydrogenase (SDH), a key enzyme in fungal respiration and energy production. SDH inhibitors are currently classified as bearing medium to high risk of resistance by the Fungicide Resistance Action Committee (FRAC Group 7).

1.3 Product claims and use pattern

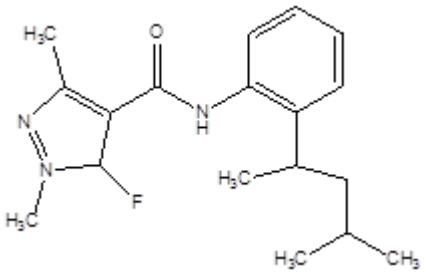
EverGol Prime Seed Treatment is intended for use as a seed treatment for the suppression of rhizoctonia root rot and control or suppression of smut diseases of wheat and barley at rates of 40-80 mL/100 kg seed (9.6-19 g ac/100 kg seed). The higher rate is to be used in situations conductive to greater risk of rhizoctonia root rot damage and/or higher yielding situations.

For application, the product is diluted with water to a total volume of 400-600mL (product plus water)/100kg seed. Treatment may be in a commercial seed treatment facility or on-farm using equipment equivalent in function to commercial seed treatment facilities. Treated seed is to be stored in clearly marked bags or other containers and kept apart from other grain.

2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

Identity

COMMON NAME:	Penflufen
IUPAC NAME:	2'-[(*RS*)-1,3-dimethylbutyl]-5-fluoro-1,3-dimethylpyrazole-4-carboxanilide
CAS NAME:	*N*-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide
CAS REGISTRY NUMBER:	494793-67-8
MANUFACTURER'S CODES:	BYF 14182
MINIMUM PURITY	950 g/kg
MOLECULAR FORMULA:	$C_{18}H_{24}FN_3O$
MOLECULAR WEIGHT:	317.41
STRUCTURAL FORMULA:	

Manufacturing site

The active constituent penflufen is manufactured by Bayer CropScience AG, at Alte Heerstrasse, D-41538, Dormagen, Germany.

APVMA active constituent standard

CONSTITUENT	SPECIFICATION	LEVEL
Penflufen	Penflufen	Not less than 950 g/kg

Physical and chemical properties of the active constituent

COLOUR:	White to off white[2]
PHYSICAL STATE:	Crystalline powder
ODOUR:	Weak
MELTING POINT:	111.1 °C (purified active); 107.6 °C (technical active)
BOILING POINT:	No boiling point at atmospheric pressure. It decomposes at approximately 300-320°C.
RELATIVE DENSITY:	1.21
pH OF 1%	6.7 (1% suspension in distilled water at 22 ºC)
SOLUBILITY IN WATER:	11.0 mg/L (pH 4) 10.9 mg/L (pH 7) 11.2 mg/L (pH 9)
SOLUBILITY IN ORGANIC SOLVENTS AT 20°C:	1,2-Dichloromethane: >250 g/L Dimethyl sulfoxide: 162 g/L Acetone: 139 g/L Methanol: 126 g/L Ethyl acetate: 96 g/L Toluene: 62 g/L *n*-Hexane: 1.6 g/L
PARTITION COEFFICIENT (*n*-OCTANOL/WATER):	log P_{ow} = 3.3 (pH 4, pH 7 and pH 9) (all 25 °C). Not pH dependent
UV/VIS ABSORPTION MAXIMA:	λ_{max} [nm] / ε [L/mol·cm] 209 / 2.37×10^4 232 / 1.09×10^4
VAPOUR PRESSURE AT 20°C:	4.1×10^{-7} Pa at 20°C 1.2×10^{-6} Pa at 25°C 1.7×10^{-4} Pa at 50°C
HENRY'S LAW CONSTANT	1.05×10^{-5} Pa×m^3×mol^{-1} at 20°C, pH 6.5 in distilled water
DISSOCIATION CONSTANT	No dissociation constant pKa found in aqueous solution in the range of 1 < pKa < 12
HYDROLYSIS	Stable to hydrolysis

[2] The colour may vary from colourless to pale (green/blue/pink) depending on the purity in the technical grade active constituent

FLAMMABILITY	Not a highly flammable solid
AUTO-FLAMMABILITY	No self-ignition temperature was observed up to the melting point or up to the maximum test temperature of 403 °C. Penflufen is not classified as a self-heating substance
EXPLOSIVE PROPERTIES	Not explosive
OXIDISING PROPERTIES	No oxidizing properties

2.2 Product

Identity

DISTINGUISHING NAME:	EverGol Prime Seed Treatment
FORMULATION TYPE:	Flowable concentrate for seed treatment (FS)
ACTIVE CONSTITUENT:	240 g/L penflufen
PACK SIZES:	5L and 10L
PACKAGING MATERIAL:	High density polyethylene (HDPE)

Manufacturing site

The product EverGol Prime Seed Treatment is formulated overseas and imported into Australia.

Physical and chemical properties of the product

APPEARANCE:	Red suspension
ODOUR:	Slight chemical odour
PH:	6.3 (1% in deionized water) 6.9 (undiluted at room temperature)
SPECIFIC GRAVITY:	1.078 g/L at 20°C
SURFACE TENSION:	41 mN/m undiluted at 25 °C
VISCOSITY:	At 20 ºC with a shear rate of 20 s^{-1}: Dynamic viscosity; ŋ = 0.1762 Pa • s Kinematic viscosity; v = 1.63×10^{-4} m^2/s At 20 ºC with a shear rate of 100 s^{-1}: Dynamic viscosity; ŋ = 0.0677 Pa • s Kinematic viscosity; v = 0.628×10^{-4} m^2/s
FLAMMABILITY:	Not flammable

EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	No oxidising properties
CORROSIVE HAZARD:	Not corrosive to HDPE container
PERSISTENT FOAM:	13 mL (after 1 min) (0.06% application concentration)
ACTIVE SUSPENSIBILITY:	100% (0.06% application concentration)
WET SIEVE TEST:	0.06% residue on a 75 micron sieve
PARTICLE SIZE DISTRIBUTION:	90 % ≤ 4.80 µm 50 % ≤ 1.72 µm 10 % ≤ 0.70 µm
POURABILITY:	Residue: 1.55% Rinsed residue: 0.11%
PRODUCT STABILITY	The product should remain within specifications for at least 2 years under normal conditions in HDPE packaging

2.3 Conclusion

The APVMA is satisfied that the chemistry and manufacture data requirements necessary for the approval of EverGol Prime Seed Treatment, containing the active constituent penflufen, have been met.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

The submitted studies on the active constituent in rats showed that it is was rapidly and completely absorbed (≈ 91% of dose bioavailable) by the oral route, widely distributed throughout the body of rats with the highest tissue concentrations detected in the liver, kidney and erythrocytes, extensively metabolised in rats and rapidly excreted. For risk assessment purposes, a dermal absorption factor of 1% was used for the diluted and undiluted product.

Penflufen is of low acute oral, dermal and inhalational toxicity in rats. It was not a skin irritant in rabbits but was considered a slight eye irritant in the same species. It was not a skin sensitiser in guinea pigs.

The systemic toxicity of penflufen in dietary studies consisted primarily of body weight and body weight gain decreases, liver toxicity such as increased liver weight and centrilobular hepatocellular hypertrophy with associated clinical chemistry changes, and thyroid effects (e.g. follicular cell hypertrophy) generally seen at higher dose levels. This systemic toxicity profile was observed in short-term, subchronic and chronic toxicity studies in rats, mice and dogs, with the available data indicating that the rat was the most sensitive species. No treatment related adverse effects were seen in a short-term dermal study in the rat at the limit dose.

Penflufen was not carcinogenic in male or female mice. In contrast, penflufen was carcinogenic in both male and female rats. An increased incidence of histiocytic sarcoma was seen in male rats only at the low, middle and high dose that was slightly greater than the laboratory control range at the low and mid dose groups and greater at the high dose group. Additionally in males, the total incidence of brain astrocytoma at the top dose level was greater than the laboratory historical control range. In female rats, an increased incidence was seen in ovarian tubulostromal adenoma at the top dose level which was greater than the laboratory historical control range.

Penflufen was not a reproductive or developmental toxicant, and tested negative *in vitro* and *in vivo* in a battery of mutagenicity and/or genotoxicity studies. Additionally, the available data was not considered to demonstrate a neurotoxic or immunotoxic hazard.

The product EverGol Prime Seed Treatment is of low acute oral, dermal and inhalational toxicity in rats. It was not a skin or eye irritant in rabbits, and was not a skin sensitiser in mice.

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of EverGol Prime Seed Treatment when used in accordance with the label instructions.

3.2 Evaluation of Toxicology

The toxicological database for penflufen, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of penflufen and characterise the risk to humans. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposure. The use of high doses increases the likelihood that potentially

significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the no-observable-adverse-effect-level (NOAEL) are used to develop acceptable limits for dietary or other intakes [acceptable daily intake (ADI) and acute reference dose (ARfD)] at which no adverse health effects in humans would be expected. Since the assessment relied significantly on international collaboration, the NOAEL and lowest-observable-adverse-effect level (LOAEL) approach was adopted with scientific justifications.

Toxicokinetics and metabolism

The absorption of penflufen was estimated following a single oral gavage administration at low and high dose levels (2 or 200 mg/kg bw) in male rats, the low dose only in female rats, and the low dose level in bile duct cannulated male rats, by measuring the radioactivity present in urine, cage wash, carcass, bile and/or faeces over 48 hours post dosing.

Two different radiolabelled forms of penflufen were used in the adsorption, distribution, metabolism and excretion studies: [phenyl-UL-$^{13}C_6$/^{14}C] and [pyrazole-3-^{14}C].

Penflufen was rapidly absorbed and quickly distributed throughout the body. Overall recovery of the total administered radioactivity in the urine, faeces, organs, tissues, gastro-intestinal tract (GIT) and/or bile was between 94-97% in both male and female rats. Absorption of radiolabelled penflufen began immediately after oral (gavage) administration and maximum plasma concentrations (C_{max}) were reached between 40 minutes and 1.5 hours (t_{max}) after dosing.

In male rats dosed with 2 mg/kg bw, the peak plasma concentration was reached within 40 minutes (0.59 - 0.74 µg/mL), in females dosed with 2 mg/kg bw the peak plasma concentration was reached within 60 minutes (0.75 µg/mL) and in males only dosed with 200 mg/kg bw the peak plasma concentration was within 90 minutes (19.19 µg/mL).

The percent absorption of radiolabelled penflufen based on recoveries of radioactivity in the bile, urine and body, excluding GIT, was ≈ 91% of the administered dose. Based on the kinetic behaviour, it is assumed that the total absorbed dose is systemically available.

The distribution pattern of radioactivity was similar between sexes. In both sexes, maximum total radioactive residues (TRR) values were reached for all organs and tissues (except nasal mucosa) at one hour after administration (t_{max}). The highest TTR was observed in the liver, kidney and erythrocytes in both male and female rats. In male rats, the values for the myocardium and adrenals were higher than in the blood. In female rats, the values for brown fat, myocardium, pancreas, most glandular organs, and the ovary and uterus were higher than in blood. These results were in agreement with the whole-body autoradiography studies that were conducted in the rat.

Penflufen was extensively metabolised in the rat. Metabolic reactions were detected in ten different positions of the molecule and a large number of metabolites were formed. The majority of metabolites (58% to 94% of the dose) were identified. The other metabolites were characterised by their extraction and chromatographic behaviour. There were no different metabolites found in males and females, but the amount of some metabolites was different with regard to sex (e.g., BYF 14182-desmethyl-dihydroxy-ketone: males ≈5% and females 17% of the administered dose). The main metabolic reactions were demethylation in the pyrazole ring or hydroxylation reactions occurring in the alkyl side chain of the phenyl ring, in the position 4' of the phenyl ring and in the methyl group at position 3 of the pyrazole ring. Of the hydroxylation reactions determined, most were detected as trihydroxy and dihydroxy compounds, with only a minor portion of the metabolites hydroxylated in only a single position.

A prominent hydroxylation reaction occurred in the 3 position of the alkyl side chain resulting in BYF 14182-3-hydroxy-butyl (Pen-3HB), a prominent metabolite in plants. This metabolite and its conjugate were identified in very low amounts only in the bile in the current study. Many metabolites that originated Pen-3HB were identified. Pen-3HB was described as a key intermediate in the rat metabolism.

Further oxidation of hydroxy groups yielded ketones or carboxylic acids. Conjugation with glucuronic acid was only detected in higher amounts in the bile. Metabolites originating from cleavage in the alkyl side chain with further oxidation were found (≈3-6% of the dose). Label specific metabolites, originating from the cleavage of the carboxamide bond or N-phenyl bond, were detected at very low concentrations in urine, bile and faeces extracts, or not at all.

In males at both dose levels, the majority of the dose (60-67%) was excreted *via* faeces. The renal excretion of male rats was ≈26-34% at 2 mg/kg, ≈34% at 200 mg/kg, and ≈21% in the bile duct cannulated male rats at 2 mg/kg. For the females, there was no significant difference between the excretion *via* urine and faeces (urinary excretion ≈47-61% of the dose and faecal excretion ≈40-61% of the dose) at 2 mg/kg. Bile duct cannulated male rats showed a high excretion *via* bile (≈70% of the recovered radioactivity), and there was no significant radioactivity present in the body at the time of sacrifice (48 hours after administration).

In the 2 mg/kg bw dose groups, the main portion of the radioactivity was excreted within the first 24 hours, and the plasma concentrations had declined to ≤1% of the maximum concentration within 72 hours post administration, indicating that no retention of residues in the body occurred. In the case of the 200 mg/kg bw test, the plasma concentration declined to 3.7% of the maximum concentration by 72 hours post administration. Administration of the high dose (200 mg/kg bw) caused a delay in excretion.

Less than 0.1% of the administered radioactivity was exhaled as $^{14}CO_2$ or other volatiles during a sampling period of 48 hours (both sexes).

At 2 mg/kg bw, the elimination of the test substance was somewhat faster for males than for females. The area under the curve ($AUC_{0-\infty}$) values for females (3.96 mg/L-hour) are approximately 1.4 times higher than for males (2.5-2.5 mg/L-hour), indicating a slightly higher systemic exposure for female rats. The mean residence time of the total radioactivity was short for both sexes at 2 mg/kg bw (≈13-14 hours).

The plasma concentrations for both sexes at 2 mg/kg bw showed a very fast elimination phase at the beginning of the test followed by a single terminal elimination phase. The plasma concentration curve of the 200 mg/kg bw group exhibited a second maximum after 48 hours possibly due to enterohepatic circulation.

Elimination half-lives were calculated based on a two-compartment model. The elimination half-life ($t_{1/2}$) in males was 23.1-23.6 hours and in females was 20.4 hours.

Two dermal absorption studies were available: an *in vivo* study in rats using EverGol Prime Seed Treatment, and an *in vitro* study in rat and human skin using another product, BYF 14182 FS 050 (flowable concentrate seed treatment containing 50 g/L penflufen). No formulation details were provided for BYF 14182 FS 050; however, it was considered reasonable in this instance to use the relative rat/human *in vitro* dermal absorptions of [^{14}C] labelled penflufen from BYF 14182 FS 050 to estimate the likely human *in vivo* dermal absorption of penflufen from EverGol Prime Seed Treatment using the *in vivo* rat data (i.e. the "triple pack approach").

For both the *in vivo* and *in vitro* study the radioactive label used was [phenyl-$^{13}C_6$/^{14}C]-BYF 14182.

In the *in vivo* rat study, following an 8-hour exposure period the amount of [^{14}C]-labelled penflufen potentially absorbable (sum of direct absorption and amount detected in the skin) ranged from 0.78% to 1.44% for the neat product (i.e. penflufen at a dose of 240 g/L), from 2.74% to 5.15% for a dilution to give a dose of 50 g/L, and from 4.00% to 5.35% for a dilution to give a dose of 1 g/L.

In the *in vitro* dermal penetration study, following a 24-hour exposure the mean total amounts of radioactivity considered to be potentially absorbable (directly absorbed + total remaining at dose site) at doses of 50 g/L, 10 g/L, and 1 g/L were 4.115%, 5.754%, and 6.516%, respectively for rat skin, with corresponding values of 0.172%, 1.449%, and 1.457% for human skin. Thus *in vitro*, the mean % of the applied dose potentially absorbable was 24-fold, 4-fold, and 4.5-fold greater in the rat skin than in the human skin for the 50 g/L, 10 g/L, and 1 g/L dose formulations respectively.

Where appropriate data were available the triple-pack formula for estimating human in vivo dermal exposure was applied:

$$\textit{in vivo}\text{ human absorption} = \frac{\textit{in vivo}\text{ rat absorption} \times \textit{in vitro}\text{ human absorption}}{\textit{in vitro}\text{ rat absorption}}$$

Consequently, as no *in vitro* dermal absorption data were available for undiluted EverGol Prime Seed Treatment (i.e. 240 g/L) a triple pack approach could not be undertaken. Thus, when using the neat product the absorption data determined in rats *in vivo* (approximately 1%) is the most appropriate data to use for risk assessment purposes.

EverGol Prime Seed Treatment will be diluted by the user between 5 and 15 times in water, therefore the end use concentrations will be between 16 g/L and 48 g/L penflufen. Thus, using the triple pack approach, the most appropriate data is the estimation of *in vivo* human absorption to 50 g/L; 0.13 - 0.30% which has been rounded up to 1% for human health risk assessment purposes.

Acute toxicity studies

Penflufen exhibits low acute oral (LD_{50} > 5000 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw) and inhalational (4-hour LC_{50} >2022.5 mg/m^3 the maximum obtainable concentration; mass median aerodynamic diameter (MMAD) ± geometric standard deviation (GSD): 4.11 µm ± 1.67) toxicity in rats. No deaths, clinical signs of toxicity or gross lesions at necropsy occurred following single oral or dermal doses at the limit dose. No deaths occurred following single inhalation exposure to the maximum obtainable concentration, though

laboured breathing patterns, irregular breathing, piloerection, reduced motility and high legged gait was observed in some animals with complete recovery observed by post exposure day 2. Penflufen was not a skin irritant in rabbits or a skin sensitiser in guinea pigs, but was a slight eye irritant in rabbits.

EverGol Prime Seed Treatment exhibits low acute oral (LD_{50} > 5000 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw) and inhalational (4-hour LC_{50} >1877 mg/m^3 the maximum obtainable concentration, MMAD ± GSD: 3.70 µm ± 2.31) toxicity in rats. No deaths, clinical signs of toxicity or gross lesions at necropsy occurred following single oral or dermal doses at the limit dose. Similarly, no clinical signs of toxicity or gross lesions at necropsy occurred following a single inhalation exposure to the maximum obtainable concentration. The product was not a skin or eye irritant in rabbits and was not a skin sensitiser in mice.

Systemic toxicity

In short-term dietary toxicity studies, systemic toxicity findings included decreased body weights, body weight gains and specific target organ toxicity. In all species tested, including the rat, mouse and dog, the primary target organ of toxicity was the liver as evidenced by changes in clinical chemistry parameters, centrilobular hypertrophy, increased liver weights and macroscopically enlarged livers. An additional target organ in beagle dogs was the thyroid, as evidenced by thyroid follicular cell hypertrophy and decreased follicular diameter in the thyroid of both sexes. However, the small group size in the dog study prevents a reliable NOAEL being identified for risk assessment purposes. From the available data the rat was the most sensitive species, and the lowest NOAEL established in the short term oral toxicity studies was 12/13 mg/kg bw/d in male/female rats based on decreased body weight and food consumption at study termination.

In a short-term dermal study in the rat, the only finding was an increased incidence of thymic debris (minimal severity) in both sexes at the limit dose. This lesion was characterized by the increased presence of fragmented thymic cortical lymphocytes noted within tingible body macrophages. However, this finding was not accompanied by a decrease in the size or weight of the thymus or changes in lymphocyte counts, and it is noted that penflufen was not considered to have an immunotoxic potential in a rat immmunotoxicity study (see below). Consequently, while the significance of the finding at the limit dose is not known, it is not considered to be adverse. Thus, a NOAEL of 1000 mg/kg bw/d (the limit dose) was identified in male and female rats in this short-term dermal study.

In subchronic dietary toxicity studies, similar findings were observed as in the short-term toxicity studies with systemic toxicity continuing in the liver and thyroid. Changes in haematology and clinical chemistry parameters were also observed. The liver findings were similar to those observed in the short-term studies, and included increased organ weight and hypertrophy. The thyroid toxicity observed in rats manifested as follicular cell hypertrophy and colloid alterations. In dogs, increased adrenal weights and an increased incidence of slight diffuse cortical hypertrophy/hyperplasia in the adrenals was also observed. As for the short-term oral studies, the lowest NOAEL was established in the rat, 9.3/11.4 mg/kg bw/d in male/female rats in a 90-day oral study. This NOAEL was based on decreased body weight gain in females, along with decreased total bilirubin and increased cholesterol, liver weights and associated centrilobular hepatocellular hypertrophy in both sexes.

Chronic toxicity and carcinogenicity

In the chronic dietary toxicity study in dogs, findings were similar to those seen in the 90-day dietary study in dogs, with an increased number of effects seen on clinical chemistry parameters along with thyroid follicular cell hypertrophy. In the dietary carcinogencity study in the mouse, liver and thyroid effects were also seen, along with decreased kidney weight associated with unilateral fibrosis/atrophy in the kidney. No increased incidence was seen in any tumour type in male or female mice. In contrast, penflufen was carcinogenic in both male and female rats.

In the dietary chronic/carcinogenicity rat study, non-neoplastic liver findings with associated clinical chemistry changes were seen as in the short-term and sub-chronic studies, with effects on the thyroid also seen at highest dose levels. At the highest dose level, hepatocellular single cell necrosis and hepatocellular degeneration/necrosis was also seen in both sexes. this finding supports the proposal that that while an adaptive response (i.e. hepatocellular hypertrophy) was seen in the liver at low dietary dose levels, at higher dose levels the presence of changes in associated clinical chemistry parameters suggest that a toxic effect secondary to the adaptive response is occurring in the liver (i.e. observed liver effects are now considered adverse).

In relation to treatment related neoplastic findings, an increased incidence of histiocytic sarcoma was seen in males only at 100, 2000 and 7000 ppm (5%, 5% and 8.3% respectively) that was greater than both the concurrent control (0%) and historical control range (1.7 - 3.3%). Additionally in males, the total incidence of brain astrocytoma at 7000 ppm was greater than both the concurrent control (1.7%) and historical control range (1.7 – 3.7%). In female rats, an increased incidence was seen in ovarian tubulostromal adenoma at 7000 ppm (12%) which was greater than the concurrent control (3.3%) and historical control range (1.7 – 6.7%).

The neoplastic findings in male rats observed up to and including the top dose level of 7000 ppm were seen at dose levels that did not exceed the maximum tolerated dose (e.g. no treatment related effect was seen on survival rate, and the overall body weight and body weight gain decrease at 7000 ppm was just 4% and 5% respectively). No mode of action (MOA) was proposed or established for either of these tumour types. In females, at the top dose of level of 7000 ppm, while no effect was seen on the survival rate an overall decrease in body weight of 12% was seen along with a decrease in body weight gain of 18% which was largely due to a decrease of 58% in weeks 1 – 2. Thus, this data indicates the top dose level has produced evidence of toxicity and the maximum tolerated dose (MTD) has been exceeded. However, the MTD was not significantly exceeded and, furthermore, these rare tumour findings, for which no MOA was proposed or established, are unlikely to be associated with the observed evident toxicity (i.e. are considered unlikely to be secondary to the observed toxicity). Thus, penflufen was also considered to be carcinogenic in female rats.

A no-observable-effect-level (NOEL) of 100 ppm (5.6 mg/kg bw/day) was established in female rats based on hepatocellular hypertrophy, hepatocellular macrovacuolation, decreased total bilirubin, hepatocellular brown pigment and hepatocellular alteration. However, a NOAEL could not be established in rats and, thus, the LOAEL was established at 4 mg/kg bw/d (100 ppm) in male Wistar rats based on a treatment related increase in the incidence of histiocytic sarcomas.

Genotoxicity

Penflufen has been evaluated in a comprehensive battery of seven genotoxicity assays comprising of two *in vitro* bacterial and two mammalian gene mutation assays, two *in vitro* mammalian chromosome aberration assays and an *in vivo* micronucleus assay. The *in vitro* assays were performed with and without an exogenous metabolic activation system derived from rat liver. In both the *in vitro* and *in vivo* assay(s), penflufen did not demonstrate a mutagenic and/or a genotoxic potential at the limit dose and/or in the presence of cytotoxicity. Thus, penflufen is considered not to be an *in vivo* genotoxicant.

Reproductive and development toxicity

In a dietary two generation study in rats, the parental systemic NOAEL was 1000 ppm (64 mg /kg bw/day in males and 75.9 mg /kg bw/day in females), based on decreased body weight, decreased body weight gain, alterations in food consumption, decreased thymus weight in both genders, and decreased spleen weights in females (both generations) at 4000 ppm (252.2 mg /kg bw/day in males, 294.5 mg /kg bw/day in females). The reproductive NOAEL was 1000 ppm (75.9 mg/kg bw/day) based on decreased litter size observed in F_1 and F_2 pups (Day 0) at 4000 ppm (9.2 [↓13%] and 9.3 [↓11%] respectively, which was just outside the historical control range [9.4 - 12.8]).

In offspring, decreased pup body weight and pup body-weight gain, delayed vaginal patency, and decreased spleen weights were also seen at 4000 ppm (256.5 mg/kg bw/day in males, 293.4 mg/kg bw/day in females).

The delayed vaginal patency in F_1 (39.6 days) and F_2 females (39.8 days) was outside the historical control range (33.4-36.0 days). On the day of vaginal opening a 1% increase in body weight was seen in F_1 females and a 7% decrease in F_2 females. Thus, this delay in sexual maturation was not associated by a decrease in offspring body weight. However, vaginal opening (and the other observed effects in offspring) was observed in the presence of maternal toxicity (8%-10% decrease in body weight and a 14%-15% decrease in body weight gain seen in dams of both generations throughout gestation). Furthermore, it is noted that the decrease in vaginal opening in F_1 offspring was not associated with any additional effect on reproductive parameters in F_1 adults that was not already observed with the P_1 parental animals.

The observed reproductive toxicity (slight decrease in litter size) and effects in offspring were considered to be a secondary non-specific consequence of maternal toxicity.

In an oral (gavage) developmental toxicity study in rabbits, does at 600 mg/kg bw/day showed a mean body weight loss of 0.01 kg initially [gestation day (GD) 6 to 8] compared to a mean maternal body weight gain of 0.02 kg in the controls. Thereafter, mean maternal body weight gain was reduced (↓60% to ↓71%) at several time intervals between GD 8 and 22 and overall (GD 6 to 29; ↓26%). All groups displayed a negative corrected body weight change, but the mean maternal corrected body weight change at 600 ppm was larger (-0.29 kg) than that of the control (-0.20 kg). Consistent with the reduced body weight gain, mean maternal food consumption was reduced at 600 mg/kg bw/day (18% to 27%) throughout most of the study (GD 6 to GD22). The only treatment related and adverse finding in foetuses, was an increased incidence of parietal (uni/bi) split in litters (16.7%, historical control range [hc] 0 – 4.2%) and foetuses (3.3%, hc 0 – 9.0%), and single (uni) branched ribs in litters (11.1%, hc 0 – 9.1%) and foetuses (1.2%, hc 0 – 1.0%), at 600 mg/kg bw/d. All other observed skeletal findings were within the historical control range. Additionally, the observed limited minor skeletal findings were considered to be a secondary non-specific consequence of the observed

marked maternal toxicity (i.e. as indicated by the magnitude of the observed decrease in body weight and body weight gain over the dosing period). Thus, penflufen was not considered to be a developmental toxicant in the rabbit.

No evidence of a developmental toxicity potential was seen in an oral (gavage) developmental toxicity study in female rats up to and including dose levels that produced marked maternal toxicity (e.g. overall body weight gain (GD 6-21) at the top dose of 300 mg/kg bw/day was 13% lower than controls, and the corrected body weight gain was 19% lower during this period.

The lowest NOAEL for both maternal; and developmental toxicity was established at 100 mg/kg bw/d in rabbits. The maternal NOAEL was based on decreased body weight gain and food consumption at 600 mg/kg bw/d. The developmental NOAEL was established at 100 mg/kg bw/day based on minor skeletal finding at 600 mg/kg bw/d: increased incidences of parietal (uni/bi) split and one rib (uni): branched.

Neurotoxicity

In an acute oral (gavage) neurotoxicity study in rats, a NOAEL of 50 mg/kg bw was identified in females based on decreased motor and locomotor activity at 100 mg/kg bw. In males, a NOAEL of 100 mg/kg bw was established in male rats based on the same findings and urine staining at 500 mg/kg bw. In each sex the findings in these two functional observation battery (FOB) parameters was transient, being observed on the day of observation and absent at the next FOB analysis on day 7 post administration. In a 90-day dietary neurotoxicity study, there were no consistent findings during the FOB analysis, though motor activity was sometimes slightly reduced in females at 516 mg/kg bw/d (albeit in the presence of systemic toxicity as indicated by decreased body weight and body weight gain), which is consistent with the findings following acute exposure. No effect on FOB parameters was seen in males, and in both the acute and sub-chronic neurotoxicity study no histopathological changes to the nervous system were observed.

The observation of slight decreases in a FOB parameter (i.e. motor activity) in females at higher dose levels in the subchronic study compared to the acute study could potentially be due to the method of application i.e. gavage versus dietary. However, overall, the available data from the two studies is only considered to provide evidence of a weak neurotoxicity potential evident following gavage administration.

Immunotoxicity

In a short-term dietary immunotoxicity study in rats, there were no treatment-related effects on spleen or thymus weights or total spleen cell counts, and the plaque-forming assay showed no evidence for treatment-related effects, though this study did not perform a Natural Killer (NK) cells activity assay.

Evaluation of the available toxicity database on penflufen revealed that decreased thymus weights in males were observed at 7000 and 14000 ppm in a rat 90-day oral toxicity study. Decreased thymus and spleen weights were observed at 4000 ppm of parental and offspring of both sexes in a rat reproduction study. However, the decrease in thymus weight was considered a secondary effect due to decreased body weight; the relative thymus weight was not significantly different from the control. In addition, the toxicology database of penflufen indicates that the target organs are the liver and thyroid. The overall weight of evidence suggests that this chemical does not directly target the immune system. Therefore, NK cell activity assay is not required at this time. Thus, the immunotoxicity NOAEL is 7000 ppm (755.6 mg/kg/day for males and 960.5 mg/kg/day for females) and a LOAEL was not established.

Studies on Metabolites

Studies were conducted on two key soil metabolites. Pen-3HB which was also a key intermediate in the rat metabolism, and BYF 14182-3-pyrazolyl-AAP which was not detected in the rat metabolism studies.

BYF 14182-3-hydroxy-butyl (Pen-3HB)

In a rat oral toxiciokinetic study with Pen-3HB, the absorption of Pen-3HB began immediately after administration. The maximum equivalent concentration in plasma (C_{max} ≈0.57µg/mL) was reached 40 minutes (0.67 hours) after dosing (t_{max}). The renal excretion accounted for 25% of the administered dose, with the majority of the radioactivity (75%) being excreted in the faeces. Low amounts (0.34% of administered dose) of residue were found in organs and tissues at sacrifice 72 hours after administration. Based on these observations, the biokinetic behaviour of Pen-3HB and penflufen was very similar. Additionally, Pen-3HB was extensively metabolized in the rat with metabolic reactions were observed in the same structural positions as detected for penflufen.

Thus, the very similar biokinetic and metabolic behaviour of Pen-3HB and penflufen in rats shows that the metabolism of penflufen proceeds *via* Pen-3HB as a key systemic intermediate.

The mutagenic/genotoxic potential of Pen-3HB was investigated in an *in vitro* bacterial and mammalian gene mutation assay and an *in vitro* mammalian chromosome aberration assays. The *in vitro* assays were performed with and without an exogenous metabolic activation system derived from rat liver. Pen-3HB did not demonstrate a mutagenic or a genotoxic potential at the limit dose and/or in the presence of cytotoxicity.

BYF 14182-pyrazolyl-AAP

The mutagenic/genotoxic potential of BYF 14182-pyrazolyl-AAP was investigated in an *in vitro* bacterial and mammalian gene mutation assay and an *in vitro* mammalian chromosome aberration assays. The *in vitro* assays were performed with and without an exogenous metabolic activation system derived from rat liver. BYF 14182-pyrazolyl-AAP did not demonstrate a mutagenic or a genotoxic potential at the limit dose and/or in the presence of cytotoxicity.

3.3 Public Health Standards

Poisons Scheduling

The delegate to the Secretary of the Department of Health and Ageing sought advice from the Advisory Committee on Chemical Scheduling (ACCS) on the scheduling of penflufen. Penflufen was discussed at the June 2012 meeting of the ACCS. The delegate noted the ACCS discussion on penflufen and made an interim decision on the 5th September 2012 to include penflufen in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with no cut-off, along with an implementation date of 1st January 2013. The delegate's final decision made on 10th October 2012 confirmed that penflufen be included in Schedule 5 of the SUSMP with no cut-off, along with an implementation date of 1st January 2013.

NOAEL/ADI/ARfD

The ADI is that quantity of an agricultural or veterinary chemical which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOAEL obtained in the most sensitive species. This NOAEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The toxicological database for penflufen included several long-term oral and carcinogenicity studies in the mouse and rat, as well as a 12-month study in beagle dogs, and was considered complete. The critical health effect for penflufen was an increase in the incidence of histiocytic sarcomas in male rats in the 104 week chronic oral toxicity/carcinogenicity study. A NOAEL was not established for this health effect i.e. LOAEL = 4 mg/kg bw/d. Thus, noting the health effect and the absence of a NOAEL, an additional safety factor to the default safety factor of 100 (to account for potential intraspecies and interspecies variation) is justified.

However, the incidence of histiocytic sarcomas was only just outside the laboratory historical control range at 4 mg/kg bw/d (5% [3/60] compared to a control range of 1.7 – 3.3%) and the incidence was the same at the next highest dose of 79 mg/kg bw/d (and 8.3% at 288 mg/kg bw/d). Thus, noting the incidence of these tumours did not increase from 4 to 79 mg/kg bw/d (i.e. the dose response curve is flat) which is only just outside the historical control range, it likely that the LOAEL will be relatively close to the NOAEL. The historical control range was only based on three studies, and while it is possible that a larger historical control data base could lead to a higher upper limit for these tumor types in males the limited historical control data base for the laboratory is the key data in interpreting the relevance of the observed tumour findings. Additionally, though a MOA has not been proposed/established for this (or the other) tumour type(s) there is no evidence to suggest that the tumours arise *via* a genotoxic mechanism (i.e. a threshold response is considered to exist for the observed tumour types). Furthermore, this tumour finding was only seen in one sex and, while no histiocytic sarcomas were seen in penflufen treated females, it was observed in 3/60 (5%, the same incidence as seen in males receiving 4 and 79 mg/kg bw/d) of concurrent control females. Consequently, overall, it was considered reasonable to refine the additional default safety factor of 10 down to a value of 2.

Thus, the ADI is established at 0.02 mg/kg bw/d using the LOAEL of 4 mg/kg bw/d from a 104 week dietary chronic/carcinogenicity study in male rats and applying a 200 fold safety factor (consisting of a 10-fold safety actor for both intra- and inter-species variation and a 2-fold safety factor to account for the use of a LOAEL which is considered likely to be close to the NOAEL for the critical health effect).

The ARfD is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated event. The ARfD is derived from the lowest NOEL as a single or short-term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

An ARfD was established since penflufen was considered likely to present an acute hazard to humans. Adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available.

The lowest appropriate NOAEL from single dose studies and short term studies is 50 mg/kg bw in females from an acute neurotoxicity study in rats. This NOAEL is based on decreased motor and locomotor activity observed only on the day of treatment (at 100 mg/kg bw/d), with the same findings seen in males at a higher dose level. No histopathological changes to the nervous system were observed in either sex. Thus, a default safety factor of 100 was considered sufficient for the observed weak neurotoxic potential. Thus, the ARfD is established at 0.5 mg/kg bw using a default safety factor of 100 to account for potential intraspecies (10-fold safety factor) and interspecies (10-fold safety factor) variation.

3.4 Conclusion

The APVMA is satisfied that the proposed use of EverGol Prime Seed Treatment, containing the active constituent penflufen, is not likely to be harmful to human beings if used according to the product label instructions.

4 RESIDUES ASSESSMENT

4.1 Introduction

During residues assessment for penflufen, plant and animal metabolism studies, analytical methods and storage stability, supervised residue trials, crop rotation studies and trade aspects were considered and details are provided below.

4.2 Metabolism

Metabolism studies were conducted in potatoes, wheat, soybean, rice, confined rotational crops (wheat, soybean and turnip), laying hens and lactating goats.

In potatoes, application of [pyrazole-3-^{14}C] or [phenyl-UL-$^{13}C_6$-^{14}C] labelled penflufen was made using tuber treatment at rates of 5 g ac/100 kg tubers or in-furrow treatment at rates of approximately 540 g ac/ha. In both studies, parent compound was the most significant identified metabolite in edible commodities, being found at 20-22% of TRR in potato tubers from the tuber treatment plots and 19-28% of the TRR in potato tubers from the in-furrow plots.

Spring wheat seed was treated with [pyrazole-3-^{14}C] or [phenyl-UL-$^{13}C_6$-^{14}C] labelled penflufen at rates of approximately 5.3 (1×) and 52 (10×) g ac/100 kg seed. In the 1× experiment the most significant identified component of the residue was BYF 14182-3-hydroxybutyl-malonyl-glucoside, which comprised 20-35%, 28-35%, and 21-26% of the TRR in forage, hay and straw, respectively. The next most significant metabolite was BYF 14182-4-hydroxybutyl-malonyl-glucoside, which comprised 17-20%, 10-15%, and 9-14% of the TRR in forage, hay and straw, respectively. In straw, BYF 14182-3-hydroxybutyl-glucoside was also a major metabolite, present at 8-10% of the TRR. Parent compound was observed at very low amounts in forage and hay (≤1.4% TRR). No identification or characterisation of residues in wheat grain was conducted due to the low levels of residue found.

In soybean, seed treatment application of [pyrazole-3-^{14}C] or [phenyl-UL-$^{13}C_6$-^{14}C] labelled penflufen was made at rates of approximately 5.1 (1×) and 50 (10×) g ac/100 kg seed. Two major metabolites were identified in soybean forage: BYF 14182-homoglutathione (Pen-HGT) at 57-59% of the TRR and BYF 14182-cysteine at 10-13% of the TRR. Parent compound was found at low levels in forage (≤2.1% of the TRR). In hay, there were only two metabolites detected, BYF 14182-3-hydroxybutyl-malonyl-glucoside at 37-38% of the TRR and Pen-HGT at 21-46% of the TRR. Parent compound was also significant in hay in the phenyl-label study, at 24.1% of the TRR. Similarly, in seed, only two major metabolites were detected, BYF 14182-desmethyl-dicarboxylic acid at 65.1% of the TRR in the pyrazole-label study and Pen-HGT at 22.5% of the TRR in the pyrazole-label study and 77.3% of the TRR in the phenyl-label study.

Application of [pyrazole-3-^{14}C] or [phenyl-UL-$^{13}C_6$-^{14}C] labelled penflufen was made to paddy rice by soil application at transplanting at approximately 500 g ac/ha. The most significant identified residue component in kernels was parent at 20-31% of the TRR with Pen-3HB comprising 20-23% of the TRR. In rice husks, the two most significant components were parent at 26-28% of TRR and Pen-3HB at 23-31% of TRR. Rice straw had the most complex and extensive metabolic profile of the three matrices in both label studies. Parent and ten (pyrazole-label) or seven metabolites (phenyl-label) were identified. None of the residue components

exceeded 10% of the TRR all were above 0.01 mg/kg. The largest identified components of the residue in straw were BYF 14182-succinyl-cysteine-glycine and BYF 14182-sulfonic acid, both at approximately 6% of the TRR in both studies.

The metabolism in all plants was extensive and similar. The main reactions involved were hydroxylation at the 3-position of the alkyl chain and conjugation of the hydroxyl group with glucose and malonic acid, conjugation with homoglutathione or glutathione *via* substitution of the fluorine atom followed by metabolic degradation of the glutathione moiety and cleavage of the carboxamide bond and N-demethylation and oxidation of the methyl group in the pyrazole moiety.

Confined rotational crop studies with [pyrazole-3-^{14}C] or [phenyl-UL-$^{13}C_6$-^{14}C] labelled penflufen in rotational crops were performed in wheat, soybeans, turnips or Swiss chard at either 500 g ac/ha or 10 g ac/ha. Overall, the metabolism in rotational crops was extensive and similar to primary crops. The main reactions were hydroxylation at the 3- and 4-position of the alkyl side chain followed by conjugation with glucose and malonic acid and conjugation with glutathione or homoglutathione *via* substitution of the fluorine atom followed by metabolic degradation of the glutathione/homoglutathione moiety. In rotational crops, cleavage of the carboxamide bond releasing a pyrazole carboxylic acid moiety followed by N-demethylation and oxidation of the remaining methyl group to a second carboxylic acid group followed by decarboxylation and conjugation with serine and also cleavage of the N-phenyl bond releasing the pyrazole-4-carboxamide which was further metabolized *via* N-demethylation were more common than in the primary crops. Metabolism studies in rotational crops performed at 500 g ac/ha indicate that Pen-3HB and conjugates represent the major portion of the residues in the rotational crops. The parent compound was found only in relatively small amounts in several of the crops. Cleavage products, represented by BYF 14182-pyrazole-carboxamide and BYF 14182-bis-desmethyl-3-carboxylic acid (Pen-D3C), are more common in the rotational crops than in the primary crops. Metabolism studies on rotational crops performed at 10 g ac/ha indicate that the metabolism in rotational crops at this lower rate is qualitatively similar to the metabolism at the higher rate.

Metabolism studies in which laying hens were administered mean daily doses of [pyrazole-3-^{14}C] or [phenyl-UL-$^{13}C_6$-^{14}C] labelled penflufen (approximately 2 mg per kg bw/day corresponding to 26 ppm dry feed /day) showed that parent penflufen was identified in eggs (5-12% TRR) and fat (74-78% TRR). The metabolite penflufen-3,4'-dihydroxy-glucuronide was present in liver at 5-7% TRR.

Metabolism studies in which lactating goats were administered mean daily doses of [pyrazole-3-^{14}C] or [phenyl-UL-$^{13}C_6$-^{14}C] labelled penflufen (approximately 2 mg per kg bw/day corresponding to 48 ppm dry feed /day) showed that parent penflufen was identified in evening milk (1.1% TRR, 0.001 mg/kg in the pyrazole label only), muscle (1.0% TRR, <0.001 mg/kg in the pyrazole label only) and fat (43% TRR, 0.006 mg/kg in the pyrazole radiolabel, 19% TRR, 0.003 mg/kg in the phenyl radiolabel). The metabolite penflufen-3,4'-dihydroxy-glucuronide was observed in liver at 10-15% TRR and in kidney at 10-13% TRR for both studies.

Based on the available plant and animal metabolism data, it is concluded that:

- Although parent penflufen was the major component of some matrices such as potato tubers and was observed in all rice matrices, it was not observed in all plant tissues (for example wheat hay) and in some of those in which it was observed (such as in wheat forage and straw), it was present only as a minor or insignificant component. The results of the metabolism studies on spring wheat however

suggest that it is very unlikely that residues of penflufen or any metabolite in wheat grain will exceed 0.01 mg/kg when used according to the proposed good agricultural practice (GAP). A residue definition of parent compound is proposed for penflufen in commodities of plant origin, for both maximum residue limit (MRL) enforcement and dietary risk assessment.

- The hen metabolism studies showed that penflufen was the only identified compound in fat (for both labels). It was also identified in eggs. The metabolite penflufen-3,4'-dihydroxy-glucuronide was present in liver in both labels. The goat metabolism studies showed that penflufen was identified in milk, muscle and in larger amounts in fat. The metabolite penflufen-3,4'-dihydroxy-glucuronide was observed in liver and in kidney in both labels. A residue definition of penflufen is proposed for penflufen in commodities of animal origin, for both MRL enforcement and dietary risk assessment.

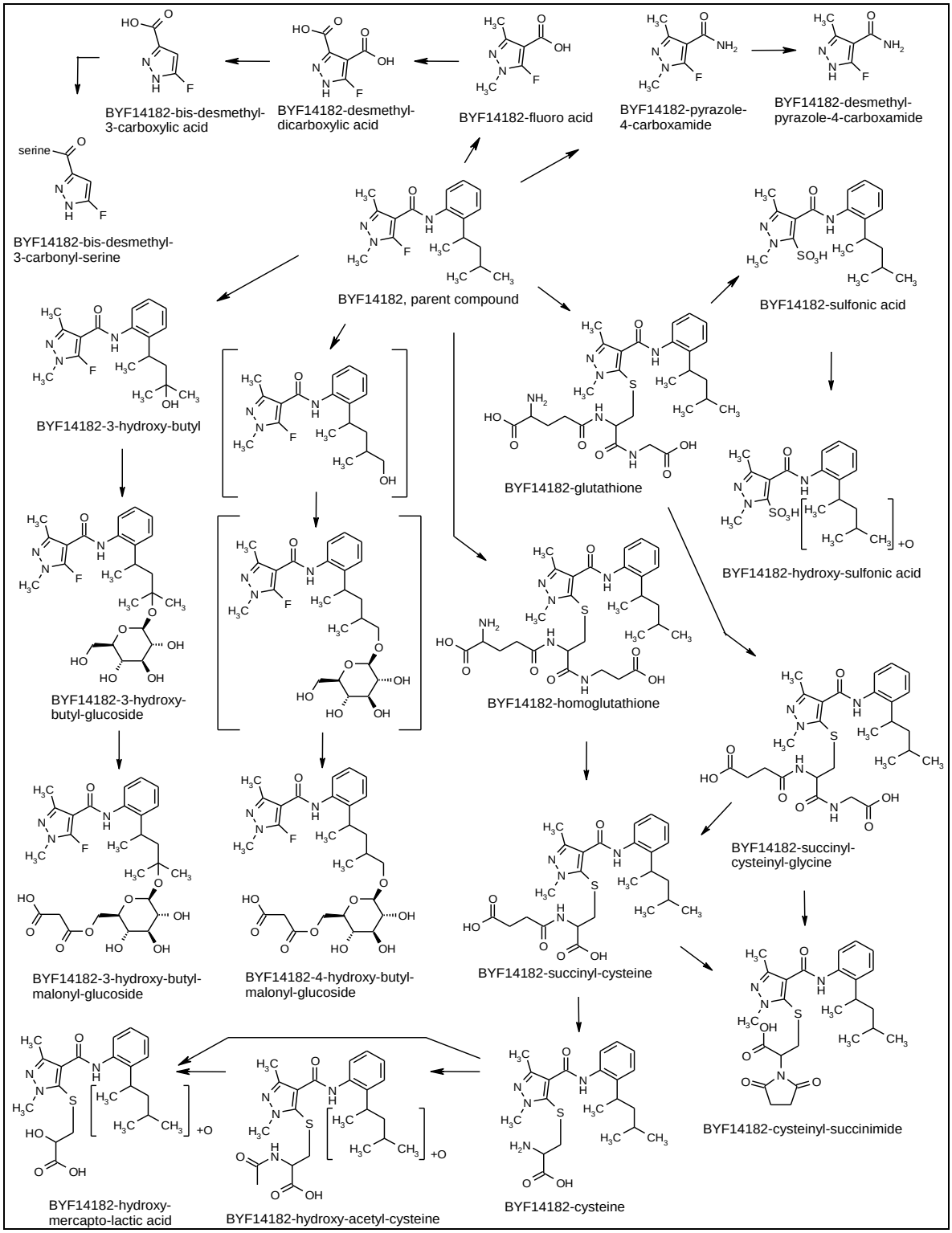


Figure 1: Metabolism of Penflufen in Plants

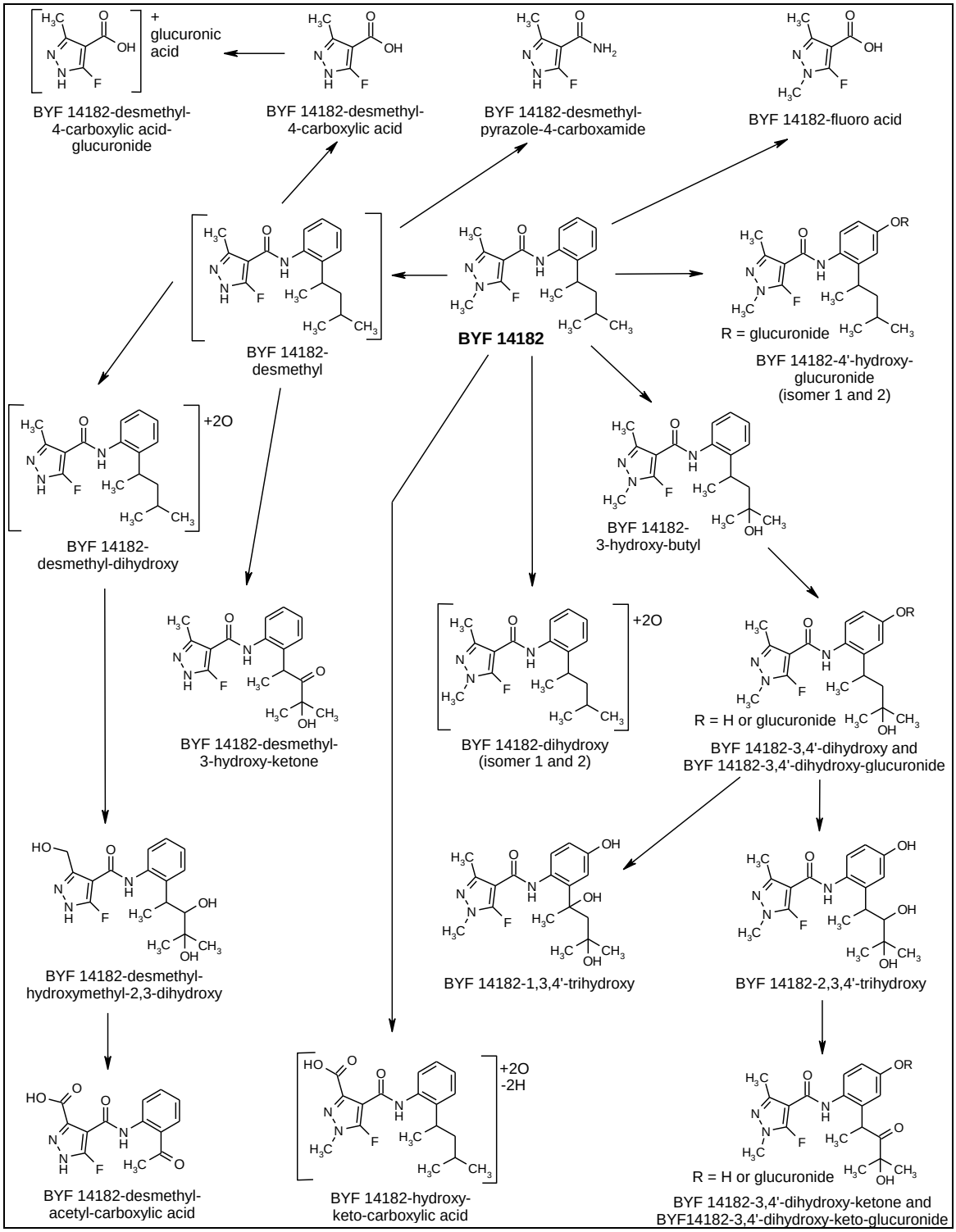


Figure 2: Metabolic pathway of Penflufen in the Laying Hen

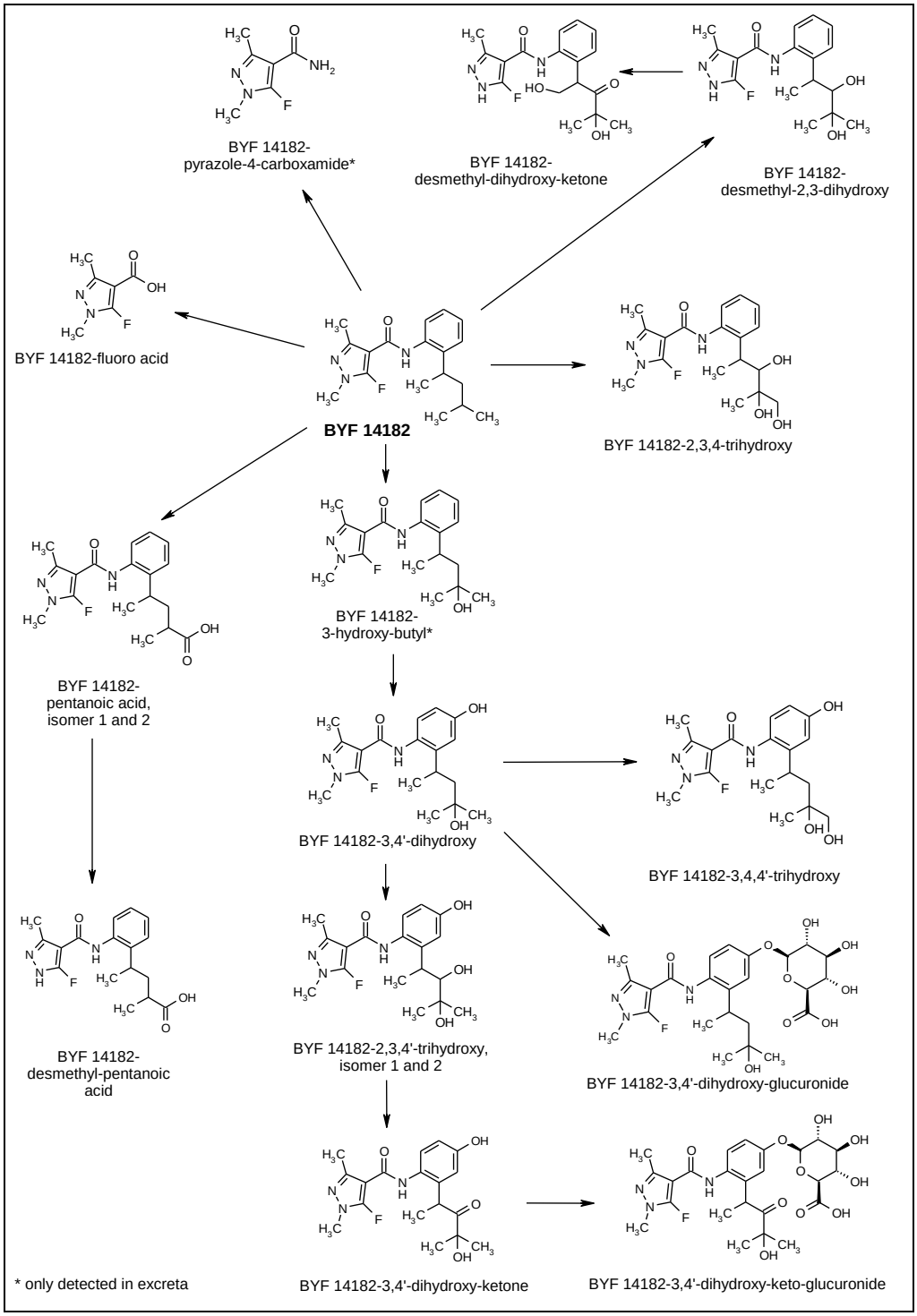


Figure 3: Metabolism of Penflufen in Livestock

4.3 Analytical methods

Determination of residues in plant commodities

Residue analytical methods for analysis of penflufen and metabolites Pen-3HB and its malonyl glucoside and glucoside conjugates, Pen-HGT and BYF 14182-pyrazole-4-carboxamide (Pen-PCX), in a representative range of plant commodities were also developed. Root vegetable (potato tuber and carrot root and leaf), leafy vegetable (lettuce), cereal (forage, grain and straw), pulse (dried bean), oilseed (sunflower), and fruit (orange) matrices were tested. Samples were extracted into aqueous acetonitrile and concentrated before heating with strong acid to hydrolyse the conjugates. The extracts were then neutralised, diluted and the internal standards added. Analytical methods were validated in each matrix for penflufen, Pen-3HB and Pen-PCX using the internal standard method and for Pen-HGT using the external standard method with analysis by LC-MS-MS. The limit of quantitation (LOQ) for each analyte was 0.01 mg/kg for all analytes in all matrices except barley straw for which the LOQ for all analytes was 0.05 mg/kg.

The method was found to be adequate for analysis of penflufen, Pen-3HB and Pen-PCX in plant commodities, using the internal standard method and for Pen-HGT using matrix matched external standards. Results for penflufen and Pen-3HB using matrix matched or solvent external standards are also adequate with the possible exception of orange which gave better recoveries with the internal standard method.

Determination of residues in animal tissues

Method 01192 was submitted for the determination of penflufen and its metabolite penflufen-3,4'-dihydroxy (BYF 14182-3,4'-dihydroxy) in animal tissues, milk and eggs. Samples were extracted using acetonitrile/water with blending, followed by centrifugation and filtration. Analyses were conducted using HPLC-MS-MS. Mean recoveries were between 70 and 110%. The relative standard deviations for all commodities and all fortification levels were well below 20%.

The LOQ is 0.01 mg/kg for all analytes. The method proved to be suitable to determine residues of penflufen and penflufen-3,4'-dihydroxy in animal matrices such as cow liver, kidney, muscle, fat, milk, cream and hen egg.

Storage stability

A storage stability study was conducted to investigate the storage stability of penflufen in matrices of plant origin when stored under freezer conditions. Samples of potato (tuber), lettuce (head), orange (fruit), dry bean (seed), wheat (grain and straw) and sunflower (seed) were fortified with the test items at 0.20 mg/kg (1 mg/kg for wheat straw). Samples were stored at ≤-18°C and were analysed (Method 01057) after storage intervals of 0, 3-4, 8-9, 16-17 and 26-27 months.

After a deep-freezer storage period of 26-27 months mean corrected recovery values ranged from 87 – 109% for penflufen. Penflufen is considered to be stable for at least 26 months in potato (tuber), lettuce (head), dry bean (seed), orange (fruit), wheat (grain and straw) and sunflower (seed) when stored frozen at ≤-18°C.

In the animal feeding study, samples were stored frozen for a maximum of 30 days. No storage stability studies were conducted in milk or any tissue matrices.

4.4 Residue Definition

The recommended residue definition is penflufen for the purposes of dietary exposure assessment and for compliance and monitoring.

4.5 Residue Trials

Thirteen Australian residues trials were provided in support of the proposed use. A single application was made at rates of 20, 30 or 45 g ac/100 kg of seed (1.0, 1.6 and 2.3× the maximum proposed application rate, respectively). Samples of seed were collected at the time of sowing, while samples of forage were taken nominally at 35, 42 and 49 days after sowing. Grain and straw were collected at harvest. In addition residue trials from the United States were provided in which application to wheat and barley was at approximately 5 g ac/100 kg seed. In addition, some trials were carried out at approximately 1.3× the application rate proposed for Australia.

Grain

In the Australian residue trials for wheat, barley and oats, no penflufen residues above the LOQ (0.01 mg/kg) were detected in grain samples at harvest after application at 20 g ac/100 kg of seed (approximately 1× the maximum proposed application rate). Application to wheat, barley and oats at rates up to 2.3× the maximum proposed application rate similarly gave residues levels in grain at less than the LOQ. In the trials of penflufen on wheat undertaken in the United States at 24-35 g ac/100kg seed (i.e.1.2-1.8× the maximum proposed Australian application rate), residues of penflufen in wheat grain were <0.01 mg/kg.

Based on the results of these trials, it is recommended that an MRL for GC 0080 Cereal Grains be established at *0.01 mg/kg (*set at the LOQ).

Forage

In the submitted Australian residue trials for wheat, barley and oats, the highest residues detected in forage samples at five or more weeks after sowing after application at 20 g ac/100 kg of seed (approximately 1× the maximum proposed application rate) for each individual trial were:

> Forage of cereals (dry): <0.055, <0.055, <0.059, 0.063, <0.067, <0.071, <0.077, <0.077, 0.11, 0.13, 0.20, 0.59 and 1.76 mg/kg (supervised trials median residue = <0.077 mg/kg).

In the submitted United States trials of penflufen on wheat at 24-35 g ac/100kg seed (i.e.1.2-1.8× the maximum proposed Australian application rate), residues of penflufen found in wheat forage were <0.01 mg/kg.

Based on the results of these trials, it is recommended that an MRL for Forage of cereal grains (dry) be established at 3 mg/kg. The proposed 5 week WHP for grazing and cutting for stock food is considered appropriate.

Straw

In the Australian residue trials for wheat, barley and oats, no penflufen residues above the LOQ (0.05 mg/kg) were detected in straw samples at harvest after application at 20 g ac/100 kg of seed (approximately 1× the maximum proposed application rate). Application to wheat, barley and oats at rates up to 2.3× the maximum proposed application rate similarly gave residues levels in straw at less than the LOQ.

In the trials of penflufen on wheat undertaken in the United States at 24-35 g ac/100kg seed (i.e. 1.2-1.8× the maximum proposed Australian application rate), residues of penflufen in wheat straw or hay were <0.01 mg/kg.

Based on the results of these trials, it is recommended that an MRL for Straw and fodder (dry) of cereal grains be established at *0.05 mg/kg.

4.6 Processing studies

Processing data for cereals were not provided. No detectable residues of penflufen in cereal grain were observed at treatment rates of 1× and 2.3×. The MRL for cereal grain is sufficient to cover residues arising in processed fractions.

4.7 Crop rotation

United States

Eighteen field rotational crop trials, six wheat (cereal), six turnip (root crop) and six mustard green trials (leafy vegetables) were conducted in North America in 2008 to measure the magnitude of penflufen residues in rotational crops. The crops were planted at three plant-back intervals (1, 6 or 12-month PBIs) following a primary crop of potatoes grown from either treated seed pieces (2 g ac/ 100 kg seed) or treated seed pieces (2 g ac/100 kg seed) and in-furrow treatment (80 g ac/ha). Seeds were sown at a rate of 4000 kg seed/ha for an application rate of 80 g ac/ha for the treated seeds (approximately 4× the maximum proposed application rate) or 160 g ac/ha for the combined treated seed pieces and in-furrow application (approximately 8× the maximum proposed application rate). Residues of penflufen and its metabolites Pen-3HB, Pen-HGT, Pen-PCX, and Pen-D3C were determined.

No residues of penflufen were observed in any wheat matrix (grain, forage, straw) at any PBI (1, 6 or 12-months) from either treatment pattern (80 g ac/ha or 160 g ac/ha). Metabolites of penflufen greater than the LOQ (0.01 mg/kg) were not observed in wheat grain at any PBI at either rate. However, residues of some metabolites were observed in forage and straw (maximum 0.04 mg/kg).

In turnips, no residues of penflufen greater than the LOQ (0.01 mg/kg) were observed in the roots and tops at any PBI. Some metabolites of penflufen were observed in turnip tops (maximum 0.04 mg/kg) following treatment at 160 g ac/ha.

Residues of penflufen were not observed in mustard greens from either treatment pattern (80 g ac/ha or 160 g ac/ha). Some metabolites of penflufen, up to 0.18 mg/kg, were observed in mustard greens treated at rates of 160 g ac/ha.

Europe

In addition, three European trials were carried out to measure the magnitude of penflufen and its metabolites Pen-3HB, Pen-HGT, Pen-PCX and Pen-D3C in field rotational crops planted after around 30-days, 60-270 days or 270-365 days PBIs, following the use of penflufen in target crops. The trials were conducted in Germany, United Kingdom and Northern France. For the 30-day PBI the application was made directly on bare soil. Penflufen was applied once by spraying on bare soil with 300 L/ha water rate and 2 L/ha of test item rate (0.10 kg ac/ha) which is the highest application rate per hectare for potato in Europe. For the 60-270 day PBI (named 1st rotation) and 290-365 day PBI (named 2nd rotation) the application was made by planting potatoes treated with the formulation at a rate of 0.04 L/100 kg (corresponding to 2 g ac/100 kg). The seed density was of 5000 kg/ha corresponding to an application rate of 0.100 kg ac/ha. Potatoes were harvested at the normal time but not analysed.

Rotational crops representative of a cereal (wheat/barley), root crop (carrots) and leafy vegetable (head lettuce) were planted in the plots at various PBIs. All raw agricultural commodity samples were harvested at normal maturity. For cereals additional samples were taken at growth stage 29-30 BBCH (green material). For root and leafy vegetables additional samples were taken at early harvest (about 14 days before harvest).

After 30 days plant back interval, all residues of penflufen and its metabolites in carrot leaves and roots were less than the LOQ of 0.01 mg/kg. After the 1st rotation all residues of penflufen and its metabolites in carrot roots and leaves were less than the LOQ of 0.01 mg/kg, except for the metabolite Pen-3HB in carrot leaves with a harvest value of 0.01 mg/kg.

In lettuce heads, residues of penflufen and its metabolites were less than the LOQ of 0.01 mg/kg at all PBIs.

In cereal (winter barley or spring wheat) grain, green material and straw, residues of penflufen and its metabolites were less than the LOQ (0.01 mg/kg for grain and green material, 0.05 mg/kg for straw) at all PBIs.

It is concluded that the proposed use of EverGol Prime Seed Treatment should not result in rotational crop concerns.

4.8 Animal commodity MRLs

The applicant provided an animal feeding study designed to determine the magnitude of the residues of penflufen and penflufen-3,4’-dihydroxy that may result in mammalian tissues and milk following oral administration.

Penflufen was administered orally *via* gelatine capsules to lactating dairy cows once daily for 29 days. The target dose levels of penflufen were 1.5 mg/kg feed (1×), 4.5 mg/kg (3×) and 15 mg/kg (10×). Group 1 (control animals) received empty gelatine capsules, containing no penflufen, while Groups 2, 3 and 4 received capsules containing average actual daily doses of penflufen of 0.045 mg/kg bw/day = 1.41 ppm in feed for the 1× group, 0.130 mg/ kg bw /day for the 3× group (= 4.86 ppm in feed) and 0.438 mg/ kg bw day for the 10× group (= 15.37 ppm in feed). The cattle were milked twice daily and milk yields were recorded.

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. Additional milk from Day 25 was separated into milk fat (cream) and skim milk from the control and 10× cows that were scheduled for necropsy on Study Day 29. Ten animals were sacrificed on Study Day 29 (one control, three 1×, three 3× and three 10×) within 4 hours of the last dose. The three depuration animals of the high dose 10× group were sacrificed at Study Days 32, 36 and 43 to determine residue levels post dosing. The other control group cow was also sacrificed at Study Day 43. All tissue samples were stored frozen and remained frozen until analysis.

Residues of penflufen and the metabolite penflufen-3,4'-dihydroxy in milk, skim milk, cream, muscle, liver, kidney and fat were determined according to the validated LC-MS-MS based method.

In milk, skim milk and cream, levels of penflufen and penflufen-3,4'-dihydroxy residue were <LOQ (0.01 mg/kg) for each treatment group. No residues of penflufen or penflufen-3,4'-dihydroxy were detected above the LOQ of 0.01 mg/kg in any kidney, muscle or fat samples from the cows from the 10× dose group. In liver, residues of 0.016 mg/kg were observed for penflufen in one sample from the 10× dose group, but no residues of penflufen-3,4'-dihydroxy were observed.

No residues above the LOQ were detected in any milk or animal tissue sample at any stage during the depuration period. It is noted that depuration residues for liver were <LOQ at Day 32 and subsequent time-points.

The dietary intake of penflufen by cattle consuming cereal feed commodities resulting from the use of EverGol Prime Seed Treatment is estimated in Table 1.

The potential exposure of dairy cattle to penflufen associated with consumption of cereal grain forage is calculated to be 1.76 ppm in the feed.

The maximum residues of penflufen obtained from the penflufen feeding study, after 29 days of feeding at 15.37 ppm (8.73× the maximum animal feeding burden), were <0.01 mg/kg in milk, muscle, kidney, and fat and 0.016 mg/kg in liver.[3]

Predicted residues based on feeding at 1.76 ppm are <0.01 mg/kg in milk, muscle, live, kidney and fat.

[3] Residues were <0.01 mg/kg in liver at a feeding level of 4.86 ppm (2.76×)

It is therefore recommended that penflufen MRLs for MO 0105 Edible offal (mammalian), MM 0095 Meat [mammalian][in the fat], ML 0106 Milks and Milk fats be established at *0.01 mg/kg.

The dietary intake of penflufen by poultry consuming cereal grains resulting from the use of EverGol Prime Seed Treatment is estimated in Table 2.

The potential exposure of poultry to penflufen associated with consumption of cereal grains is calculated to be 0.01 ppm in the feed. The laying hen metabolism study showed that after 14 daily dose administrations of phenyl labelled penflufen at 1.94 mg/kg bw/day (equivalent to 25.2 ppm in the feed) or pyrazole labelled penflufen at 2.05 mg/kg bw/day (equivalent to 27.4 ppm in the feed), penflufen residues were not detected in muscle and liver, but were detected at a level of 0.077 mg/kg in fat (both labels) and at 0.012 mg/kg (phenyl label) and 0.003 mg/kg (pyrazole label) in eggs.

In the phenyl-labelled study, residues of penflufen were 0.077 mg/kg in fat and 0.012 mg/kg in eggs. Scaling down 2,738 fold to the expected residue levels of penflufen in the diet, residues are estimated to be 0.00003 mg/kg in fat and 0.000004 mg/kg in eggs. In the pyrazole-labelled study, residues of penflufen were 0.077 mg/kg in fat and 0.003 mg/kg in eggs. Scaling down 2,524 fold to the expected residue levels of penflufen in the diet, residues are estimated to be 0.00003 mg/kg in fat and 0.000001 mg/kg in eggs.

Based on the results of the poultry metabolism studies, it is unlikely that quantifiable residues of penflufen will be detected in eggs or poultry tissues. It is therefore recommended that penflufen MRLs for PE 0112 Eggs, PO 0111 Poultry, edible offal of, and PM 0110 Poultry meat [in the fat] be established at *0.01 mg/kg.

In conclusion, it is appropriate to establish penflufen MRLs of *0.01 mg/kg (*set at the LOQ) for the following animal commodities: edible offal, eggs, meat [mammalian][in the fat], milks, milk fats, edible offal of poultry, and poultry meat [in the fat].

Table 1: Cattle- 500 kg bw, 20 kg DM/day

					LIVESTOCK DIETARY EXPOSURE		
FEED COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, mg/kg	% DM	mg/animal	ppm	mg/kg bw
Forage of cereal grains	100	20	1.76 (HR)	100	35.2	1.76	0.0704
Fodder and straw of cereal grains	100	20	<0.06 (HR)	100	1.2	0.06	0.0024
Cereal grains	100	20	0.01	100	0.2	0.01	0.0004
Processed grain fractions	40	8	0.01	100	0.08	0.004	0.00016

Table 2: Poultry- 2 kg bw, 0.15 kg DM/day

					LIVESTOCK DIETARY EXPOSURE		
FEED COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, mg/kg	% DM	mg/animal	ppm	mg/kg bw
Cereal grains	100	20	0.01	100	0.0015	0.01	0.00075

4.9 Spray drift

As the proposed application to wheat and barley is *via* seed treatment only, issues of spray drift are not expected to arise.

4.10 Bioaccumulation potential

Penflufen has an octanol/water partition coefficient ($log_{10}P_{OW}$) of 3.3 at pH 4.0, 7.0 and 9.0 at pH 9. The K_{ow} log P values are greater than the cut-off (log P = 3)[4] designating a chemical as fat soluble with the potential for bioaccumulation.

In the animal feeding study conducted on lactating cattle (discussed in Section 4.8), penflufen residue levels above LOQ (0.01 mg/kg) were not observed in the milk, skim milk, cream, muscle and fat of dairy cattle subject to any treatment regime.

In the lactating goat metabolism studies, penflufen was observed in fat in both the phenyl (19% TRR, 0.003 mg/kg) and pyrazole label (43% TRR, 0.006 mg/kg) studies but not in muscle in the phenyl label metabolism study and at only 1.0% TRR (<0.001 mg/kg) in the pyrazole-labelled study. In the laying hen metabolism studies, penflufen was observed in fat in both the phenyl (92% TRR, 0.091 mg/kg) and pyrazole label (74% TRR, 0.077 mg/kg) studies but not in muscle in both studies.

Given that penflufen is fat soluble and the goat and laying hen metabolism studies (both labels for each) indicate the potential for bioaccumulation in the fat, it is recommended that the MRLs for meat (mammalian and poultry) be set 'in the fat'.

4.11 Risk assessment conclusions

The chronic dietary intake risk for penflufen has been assessed. The ADI for penflufen is 0.02 mg/kg bw/day, based upon a NOEL of 4.0 mg/kg bw/day and a 200-fold safety factor. The national estimated daily intake (NEDI) calculation is made in accordance with World Health Organization (WHO) Guidelines[5] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for penflufen is <1% of the ADI. DIAMOND Modelling[6] of chronic dietary exposure is also performed on new chemicals. The DIAMOND model estimated the chronic dietary exposure of penflufen as <1% of the ADI for the general population.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR[5] with

[4] Pesticide Residues In Food – 2005, Report pp. 27-31 (JMPR).
[5] Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.
[6] DIAMOND: The DIamond Modelling Of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ.

97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food.

The NESTIs for all relevant commodities are summarised in the following table. The highest acute dietary intake was estimated at <1% of the ARfD. It is concluded that the acute dietary exposure is small and the risk is acceptable.

It is concluded that the dietary exposure to penflufen is low and the risk from residues in food is acceptable when EverGol Prime Seed Treatment is used according to label instructions.

Table 3: National estimated short term intakes

		NESTI (% ARfD)	
	COMMODITY	2-6 years	2+ years
CG	Cereal grains	<1	<1
CF	Cereal grain fractions	<1	<1
CM	Early milling products	<1	<1
MO	Edible offal (mammalian)	<1	<1
PE 0112	Eggs	<1	<1
MM	Meat [mammalian] (10%)	<1	<1
MF	Fat, mammalian	<1	<1
ML 0106	Milks	<1	<1
FM 0183	Milk fats	<1	<1
PM 0111	Poultry, edible offal of	<1	<1
PM	Poultry meat (10%)	<1	<1
PF	Poultry fat	<1	<1

4.12 Recommendations

Amendments to the MRL Standard in Tables 4, 5 and 6 are recommended in relation to the proposed use of EverGol Prime Seed Treatment. The following withholding periods are required in conjunction to the recommended MRLs:

HARVEST WITHHOLDING PERIOD

Harvest: Not required when used as directed.

Grazing: Do not graze plants grown from treated seed or cut from stock food within 5 weeks of sowing.

Table 4: Amendments to Table 1 of the MRL Standard

COMPOUND		FOOD	MRL (mg/kg)
PENFLUFEN			
ADD:			
GC	0080	Cereal grains	*0.01
MO	0105	Edible offal (mammalian)	*0.01
PE	0112	Eggs	*0.01
MM	0095	Meat [mammalian] [in the fat]	*0.01
ML	0106	Milks	*0.01
FM	0183	Milk fats	*0.01
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat [in the fat]	*0.01

Table 5: Amendments to Table 3 of the MRL Standard

COMPOUND	RESIDUE
ADD:	
Penflufen	Penflufen

Table 6: Amendments to Table 4 of the MRL Standard

COMPOUND		ANIMAL FEED COMMODITY	MRL (mg/kg)
PENFLUFEN			
ADD:			
AS	0081	Straw and fodder (dry) of cereal grains	*0.05
AS	0080	Forage of cereal grains	3

4.13 Conclusion

The APVMA is satisfied that the proposed use of EverGol Prime Seed Treatment, containing the active constituent penflufen, will not be an undue hazard to the safety of people using anything containing its residues if used according to the product label instructions.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported and main destinations

Export commodities affected by the use of EverGol Prime Seed Treatment are wheat and barley grain and all livestock commodities derived from animals fed on wheat and barley grain, forage and straw. Wheat and barley grain and meat and dairy products are considered to be major export commodities.

In 2009/10, 13705 kilotonnes of wheat were exported, at a value of $3.686 billion. Key wheat export destinations are Indonesia, Japan, Korea, Malaysia, China and the Middle East. Australian barley (including malt) exports in 2009/10 were 4256 kilotonnes, worth $1.098 billion.

The significant export markets for animal commodities are listed in Part 5B of APVMA MORAG.[7] Total exports of dairy products in 2009/10 were worth $2.0342 billion, with key export destinations being Japan, Singapore, China, the Philippines, Thailand and the United States. Total exports of beef and veal were worth $4.144 billion in 2009/10, with the major destinations being Japan, the United States, Korea, Indonesia and Taiwan. Total exports of lamb and mutton were worth $1.4555 billion in 2009/10, with the key destinations being the United States, the European Union, Japan, and the Middle East. Overseas MRLs are established or proposed in only some overseas markets.

5.2 Overseas registration status

Similar products containing penflufen are registered for protection against certain seed-borne and soil-borne diseases on the same crops in Canada and the United States at a lower rate of application (5.0 g ac/100 kg seed):

- Pen 240FS (240 g/L penflufen, PMRA registration number 30359)
- EverGol Prime (241 g/L penflufen, USEPA registration number 264-1119); and
- PenRED 240FS (240 g/L penflufen, PMRA registration number 30360, USEPA registration number 264-1120).

In addition to uses on wheat and barley, the North American products are registered for use on various oilseed and other cereal grain crops, legume vegetables, alfalfa and potatoes.

Products containing penflufen in combination with other active constituents are also available in Canada and the United States in order to achieve effective resistance management and/or to increase the spectrum of controlled pests:

[7] www.apvma.gov.au/morag_ag/vol_3/part_05b_trade.php

- Emestro Silver (100 g/L penflufen + 18 g/L prothioconazole; PMRA registration number 30361; USEPA registration number 264-1123);
- Emestro Quantum (66.5 g/L penflufen + 207 g/L clothianidin; PMRA registration number 30362; USEPA registration number 264-1125);
- Propser EverGol (10.7 g/L penflufen + 290 g/L clothianidin + 7.15 g/L trifloxystrobin + 7.15 g/L metalaxyl; PMRA registration number 30363; USEPA registration number 264-1121);
- EverGol Energy (38.4 g/L penflufen + 76.8 g/L prothioconazole + 61.4 g/L metalaxyl; PMRA registration number 30364; USEPA registration number 264-1122); and
- EverGol Xtend (154 g/L penflufen + 154 g/L trifloxystrobin; PMRA registration number 30365; USEPA registration number 264-1124).

Codex MRLs have not have been established for penflufen.

The residue definition in the United States is penflufen. The relevant residue MRLs/ tolerances for the United States in Table 7 are established.

The proposed residue definitions in Canada are penflufen for plant matrices and for animal commodities. The relevant residue MRLs/tolerances for Canada in Table 8 have been proposed.

Table 7: Tolerances established for penflufen in the United States

COMMODITY	TOLERANCE (mg/kg)
Grain cereal, forage, fodder and straw, group 16	0.01
Grain cereal, group 15	0.01

Table 8: Proposed MRLs for penflufen in Canada

COMMODITY	TOLERANCE (mg/kg)
Cereal grains (crop group 15)	0.01
Eggs	0.01
Fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep	0.01
Milk	0.01

5.3 Potential risk to trade

The risk to Australian trade in cereal grains and grain products is considered to be low, as quantifiable residues of penflufen are not expected to be found in cereal grains from treated crops or in processed cereal commodities. The export of cereal grains should therefore not affect trade between Australia and places outside Australia.

Forage and fodder of treated crops, as well as grain, may be used as livestock feed. The overall risk to trade in animal commodities is considered to be low, as quantifiable residues are not expected to be found in the meat, offal or milk of animals given feed from treated crops. All penflufen MRLs for animal commodities are proposed to be at the limit of quantitation. Hence the export of all livestock commodities derived from animals fed on wheat and barley grain, forage and straw through the use of penflufen in EverGol Prime Seed Treatment, should not affect trade between Australia and places outside Australia.

5.4 Summary

Cereals

The available residues trial data show that quantifiable residues of penflufen are not likely to be found in wheat and barley grains from treated crops or in processed cereal commodities. The export of cereal grains should therefore not affect trade between Australia and places outside Australia.

Animal commodities

Modelling of the expected dietary burden in poultry and mammals feeding on commodities from crops treated with penflufen show that quantifiable residues are unlikely to be found in mammalian and poultry meat and offal, milk or eggs. MRLs are proposed for these commodities at the limit of quantitation. There is not expected to be any significant risk to Australian trade in meat, milk and eggs, however the APVMA welcomes comment on the proposed MRLs.

5.5 Conclusion

The APVMA is satisfied that the proposed use of EverGol Prime Seed Treatment, containing the active constituent penflufen, would not adversely affect trade between Australia and places outside Australia.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Summary

The product will be used by commercial seed treatment operators and on-farm treaters/planters (i.e. crop growers). Workers may be exposed to the product when opening containers, conducting mixing/treating procedures, bagging or transfer of treated seed, sowing of seed, and cleaning up spills and equipment. The main route of exposure to the product will be *via* the dermal and inhalational routes, although ocular exposure is also possible.

Based on available use pattern data, commercial operators are expected to treat up to 100 tonnes of seed per day, while on-farm treater/planters are expected to treat up to 27 tonnes of seed per day. Commercial users will only likely to be exposed to the product for less than 5 months of the year.

No exposure data was available with penflufen or the product, EverGol Prime Seed Treatment. However, two worker exposure studies undertaken using other products for commercial seed treatment and on-farm treater/planters (growers) were available and it was considered it is appropriate to use these studies as surrogate exposure data for estimating potential exposure to penflufen. Based on the risk assessment for workers conducting seed treatment, for both commercially and on-farm by treater/planters (growers) the margins of exposure (MOE) are all considered to be acceptable (i.e. >100). However, the surrogate exposure data relied on in this risk assessment determined the levels of exposure to workers wearing a base level of personal protective equipment (PPE). Consequently, taking into account the PPE worn during the submitted exposure studies and based on the repeat dose risk assessment, the MOEs for mixing and loading are acceptable when the operator is wearing a single layer of clothing (cotton overalls or equivalent clothing), elbow length chemical resistant gloves and impervious foot ware.

Based on the risk assessment, a First Aid Instruction and Safety Directions, along with General Safety Precautions, have been recommended for the product label.

6.2 Health hazards

Penflufen is not listed on Safe Work Australia's (SWA) Hazardous Substances Information System Database (SWA, 2012). Based on the available toxicology information, classification of the active constituent penflufen as a hazardous substance according to the National Occupational Health and Safety Commission (NOHSC) *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following human health risk phrase warranted:

Xn; R40 (Carc. Cat. 3)	Limited evidence of a carcinogenic effect

In a 104-week dietary carcinogencity study in rats, an increased incidence of histiocytic sarcoma was seen in males only at 100, 2000 and 7000 ppm (5%, 5% and 8.3% respectively) that was greater than both the concurrent control (0%) and historical control range (1.7 - 3.3%). Additionally in males, the total incidence of brain astrocytoma at 7000 ppm was greater than both the concurrent control (1.7%) and historical control range (1.7 – 3.7%). In female rats, an increased incidence was seen in ovarian tubulostromal adenoma at

7000 ppm (12%) which was greater than the concurrent control (3.3%) and historical control range (1.7 – 6.7%).

The neoplastic findings in male rats observed up to and including the top dose level of 7000 ppm were seen at dose levels that did not exceed the maximum tolerated dose (e.g. no treatment related effect was seen on survival rate, and the overall body weight and body weight gain decrease at 7000 ppm was just 4% and 5% respectively). In females, at the top dose of level of 7000 ppm, while no effect was seen on the survival rate an overall decrease in body weight of 12% was seen along with a decrease in body weight gain of 18% which was largely due to a decrease of 58% in weeks 1 – 2. Thus, this data indicates the top dose level has produced evidence of toxicity and the MTD has been exceeded. However, the MTD was not significantly exceeded. Furthermore, these rare tumour findings are unlikely to be associated with the observed evident toxicity (i.e. are considered unlikely to be secondary to the observed toxicity). Thus, penflufen was also considered to be carcinogenic in female rats.

No MOA was proposed or established for the observed tumour types in rats. However, penflufen was not mutagenic or genotoxic *in vitro* and was not genotoxic *in vivo*. Therefore, it is considered that the tumours did not arise by a genotoxic action.

No increased incidence of tumours was seen in male and female mice in a 78-week dietary carcinogenicity study. Therefore, noting that penflufen was only carcinogenic in one species (rat) and is not an *in vivo* genotoxicant, the classification as a Carc. Cat 3 mutagen is appropriate. The following cut-off's apply for penflufen:

Conc. ≥ 1%	Xn; R40 (Carc. Cat. 3)

Based on the product toxicology information and/or concentration of penflufen and other ingredients in the product, EverGol Prime Seed Treatment containing penflufen at 240 g/L is classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following human health risk phrase warranted:

Xn; R40 (Carc. Cat. 3)	Limited evidence of a carcinogenic effect.

6.3 Use pattern

EverGol Prime Seed Treatment will be applied to wheat or barley seed by fixed and mobile commercial seed treaters, or by on-farm treaters/planters. Commercial cereal seed treatment is likely to occur for up to 5 months of the year, however it is noted that various products will be used by commercial operators, only one of them being EverGol Prime Seed Treatment. Therefore, commercial users will only likely to be exposed to the product for less than 5 months of the year. Based on available use pattern data, commercial operators are expected to treat up to 100 tonnes of seed per day, while on-farm treater/planters are expected to treat up to 27 tonnes of seed per day.

6.4 Exposure during use

As EverGol Prime Seed Treatment is used specifically for seed treatment, domestic use of the product is not expected.

Bystander exposure to EverGol Prime Seed Treatment is unlikely, as seed treatment facilities are expected to use closed delivery systems and members of the public are unlikely to be present during mixing/loading activities. While post-application exposure to treated seed is a possibility through contact with treated seed or access to areas where on-farm open mixing/loading systems may be used, the potential exposure is expected to be very low.

The product will be used by commercial seed treatment operators and on-farm treaters/planters (i.e. crop growers). Workers may be exposed to the product when opening containers, conducting mixing/treating procedures, bagging or transfer of treated seed, sowing of seed, and cleaning up spills and equipment. The main route of exposure to the product will be *via* the dermal and inhalational routes, although ocular exposure is also possible.

No exposure data was available with penflufen or the product, EverGol Prime Seed Treatment. However, the applicant submitted two worker exposure studies undertaken using other products for commercial seed treatment and on-farm treater/planters (growers). One study determined worker exposure on-farm and during commercial treatment of cereal seed, and the other study determined worker exposure during commercial treatment of canola seed. In this instance, it was considered appropriate to use these studies as surrogate exposure data for estimating potential exposure to penflufen, and that based on the conduct of the worker exposure studies, reliable conclusions can be made from the data regarding exposure to workers using on-farm systems and commercial systems.

For the purpose of estimating the dermal and inhalational exposure when treating cereal seed for on-farm treater/planter operations and for commercial seed treatment operations, arithmetic means were used for total corrected dermal and inhalational exposures.

The toxic endpoint of concern and identified NOAEL is derived from repeat dose study in animals, and in this instance a MOE of 100 or above is acceptable. The MOE takes into account both interspecies extrapolation, intraspecies variability and the seriousness of the critical health effect of concern.

Based on the risk assessment for workers conducting seed treatment, for both commercially and on-farm by treater/planters (growers) the MOE are all considered to be acceptable (i.e. >100). However, the surrogate exposure data relied on in this risk assessment determined the levels of exposure to workers wearing a base level of PPE. Consequently, taking into account the PPE worn during the submitted exposure studies and based on the repeat dose risk assessment, the MOEs for mixing and loading are acceptable when the operator is wearing a single layer of clothing (cotton overalls or equivalent clothing), elbow length chemical resistant gloves and impervious foot ware.

6.5 Exposure during re-entry

Based on submitted worker exposure data for bagging of treated seed and the risk assessment for this activity, the MOE are considered to be acceptable (i.e. >100). However, the surrogate exposure data relied

on in this risk assessment determined the levels of exposure to workers wearing a base level of PPE and, thus, a general re-handling statement for when handling treated seed is recommended:

> *DO NOT allow re-handling of treated seed until dry, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.*

6.6 Recommendations for safe use

Users should follow the First Aid Instruction, Safety Directions and General Safety Precautions on the product label.

EverGol Prime Seed Treatment can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Material Safety Data Sheet.

6.7 Conclusion

The APVMA is satisfied that the proposed use of EverGol Prime Seed Treatment, when used according to the product label instructions, would not be an undue hazard to the safety of people exposed to it during its handling and use.

7 ENVIRONMENTAL ASSESSMENT

7.1 Environmental fate

Hydrolysis

Penflufen is stable in acidic, neutral and alkaline conditions, with half-lives of 0.5 – 9.5 years at pH 4 – 9. There was no significant loss of material over the test period from any of the buffer solutions.

Photolysis

In sterile buffer solutions (pH 7), penflufen slowly degrades to numerous minor transformation products (unidentified) and CO_2. The environmental phototransformation half-life of penflufen is estimated to be 83.2 days which is beyond the test period**.**

In sterilised natural water, penflufen degrades to Pen-PCX, BYF 14182-fluoro acid, and numerous unidentified minor transformation products. Formation of CO_2 and organic volatiles is negligible. The environmental phototransformation half-life of penflufen is approximately 36 days which is beyond the duration of the study.

Biodegradation

Aerobic

The metabolism of penflufen in aerobic soil was studied in six soils under laboratory conditions. Penflufen was found to be slightly to very slightly degradable with half-life values between 117 and 432 days. The major metabolite observed in soil was Pen-3HB and BYF 14182-pyrazolyl-AAP. Other minor metabolites were not identified with a total amount of up to 4% of the applied radioactivity. The aerobic degradation pathway of penflufen is firstly the hydroxylation at the alkyl side chain in the 3-position to form Pen-3HB, which is then oxidized to form BYF 14182-pyrazolyl-AAP, followed by formation of nonextractable residues and mineralization (formation of CO_2).

Field studies of penflufen were conducted in three sites in US, three sites in Canada, and six sites across Europe. Penflufen can be classified as readily to very slightly degradable under field conditions, with various DT_{50} values between 2 – 340 days (for 0 – 30 cm depth soil layer). The dissipation rates vary widely. It is also noted that for most of the field studies, even when the DT_{50} values were low, the determined DT_{90} values are high (> 1 year). These DT_{50} and DT_{90} values indicate a slowing down of the degradation of penflufen over time and some carryover of penflufen is expected after each year for most soils. Pen-3HB was not detected below 30 cm in most of the soils. BYF 14182-pyrazolyl-AAP was not detected below 15 cm for all the soils.

The three test sites in US (California, Georgia and Idaho), three sites in Canada (Ontario, Saskatchewan and Prince Edward Island), and six sites in Europe (North France, United Kingdom, Sweden, Germany, Italy and Spain) were the proposed market regions for the end-use product and most of them had history for wheat or barley crops.

In aerobic aquatic conditions (water/sediment systems) penflufen dissipates by a combination of partitioning to the sediment from the water phase and also degradation in water and sediment. The half-lives for degradation of penflufen in the complete system (sediment plus water) were 204 and 154 days (Anglerweiher), or 267 and 301 days (Hoenniger). The DT_{50} for dissipation from the water phase was 108 and 86 days for the pyrazole and phenyl labels, respectively for the Anglerweiher system. However, penflufen dissipated more rapidly in the Hoenniger system, with DT_{50} values of 5.6 and 6.1 days for the pyrazole and phenyl labels, respectively.

In an aquatic field study, penflufen was not detected in any paddy water samples excluding detections below the LOQ (0.02 ng/g) at 53 and 67 days post treatment. Penflufen had a calculated DT_{50} of 38.5 days in soil. This is considered to be consistent with the determined DT_{50} values in the aqueous photolysis studies. The transformation products Pen-3HB and BYF 14182-pyrazolyl-AAP were not detected in water samples at any sampling interval.

Anaerobic

In an anaerobic soil study, penflufen is very slightly degradable with DT_{50} values in surface water, soil and total system of 173, 990 and 866 days, respectively.

In aquatic conditions, penflufen is stable under anaerobic aquatic conditions, with dissipation from the water as the result of sorption by sediment. Penflufen dissipated with a half-life of 48.5 days in the water and was stable (calculated half-life 6.3 years) in the total system. No major transformation products were isolated, and no minor transformation products (each ≤2.5% of the applied) were identified. Nonextractable [^{14}C]-residues in the sediment increased to a maximum average of 9.2% of the applied at study termination. $^{14}CO_2$ and organic volatiles were ≤0.1% of the applied at all sampling intervals.

Based on the above results, penflufen is persistent in anaerobic conditions with dissipation in water as the result of the binding of residues to the soil.

Mobility

Penflufen has an adsorption K_d value ranged from 2.8 to 6.8 mL/g with K_{OC} values of 219-435 mL/g. Based on the K_{OC} values, penflufen has medium mobility in all the soils tested.

Metabolite Pen-3HB has an adsorption K_d value ranged from 0.3 to 1.0 mL/g with K_{OC} values of 27 – 63 mL/g. Pen-3HB is classified as highly to very highly mobile in soil.

Metabolite BYF 14182-3-pyrazolyl-AAP has a K_d values ranged from 12.3 to 26.4 mL/g with K_{OC} values of 947 – 1322 mL/g, with exception that the K_d value for a silty clay was 150.8 mL/g with a K_{OC} value of 7223 mL/g. Based on the K_{OC} values, BYF 14182-3-pyrazolyl-AAP is classified to have low mobility in all the soils tested except immobile in the silty clay.

Volatilisation is not expected to be a major route of dissipation of penflufen.

Accumulation

Penflufen is unlikely to bioaccumulate in organisms based on the determined bioconcentration factor of 100. Penflufen could potentially accumulate in soil based on the high DT_{90} values at many of the test field sites.

7.2 Environmental Effects

Avian

Avian were not sensitive to penflufen with LD_{50} values being > 2000 mg/kg bw for acute oral tests and being > 8900 mg/kg feed for dietary tests to birds. No adverse effects on ducks and bobwhite quail were observed in the 21-22 weeks reproduction studies at levels up to 946 mg/kg feed.

Mammals

Mammals were not sensitive to penflufen with an acute oral LD_{50} being > 5000 mg ac/kg bw for female rats.

Fish

Penflufen is considered to be highly acutely toxic to fish with a 96h LC_{50} of 0.103 mg/L for the most sensitive species carp. The 35d NOEC is 0.0234 mg/L for fathead minnow.

Aquatic invertebrates

Aquatic invertebrates were acutely sensitive to penflufen with a 96h EC_{50} of 1.3 mg ac/L for oyster as the most sensitive species, and a 48h EC_{50} > 4.66 mg/L for daphnids. The 21d NOEC is 1.53 mg/L for *Daphnia magna*.

Algae and aquatic plants

Algal and aquatic plants were potentially acutely sensitive to penflufen with a 96 h E_rC_{50} of > 5.1 mg/L for algae. The 7d EC_{50} is > 4.7 mg/L and the NOEC is 2.4 mg/L for duckweed.

Terrestrial invertebrates

Earthworms, and bees were not found to be sensitive to penflufen to the level tested. In the case of bees the LD_{50} is > 100 µg/bee for acute contact and oral exposure. For earthworms, the 14 d acute LC_{50} was > 1000 mg/kg dry weight soil. The 56d NOEC is 57.8 mg/kg dry soil for earthworms.

The LR_{50} (reproduction) of the formulation EverGol Prime Seed Treatment for non-target arthropods is determined to be > 250 g ac/ha for *Aphidius rhopalosiphi* and *Typhlodromus pyri*.

Micro-organisms

No long-term influence on the soil nitrogen and carbon transformation was observed at the end of the 28-day incubation period at application rates up to 3.3 mg/kg dry soil that is equivalent to 2.5 kg/ha.

Terrestrial Plants

No adverse effects at or above 25% as compared to the control for all the plant species were observed after a pre-emergent or a post-emergent application at 250 g ac/ha.

7.3 Risk Assessment

The application rate for penflufen is assumed to be of 29 g ac/ha based on an assumption of 150 kg seed/ha for the sowing rate and maximum application rate of 19 g ac/100 kg seed, which is considered to be the worst case scenario.

Given the use pattern of the product is for seed treatment, the risk for the exposure to penflufen and its metabolites was assessed for both terrestrial organisms and aquatic life. For the aquatic risk assessment, runoff modelling used conservative considerations for the worst case scenario. No unacceptable potential risk to the aquatic life was predicted from the modelling. The assessment for the leaching of the active constituents to groundwater was conducted using a model and it is not considered an unacceptable risk. Therefore, the proposed application of the product EverGol Prime Seed Treatment is not considered to pose an unacceptable risk to the aquatic compartment.

The risk for the exposure of the product to terrestrial organisms, including mammals, birds, bees, micro-organisms, macro-organisms, non-target arthropods and plants was assessed based on the available endpoints and proposed application rate of the product. The assessment shows that the risk from the proposed use and application rate of the product will be acceptable to terrestrial organisms.

7.4 Conclusions

The APVMA is satisfied that the proposed use of the new product EverGol Prime Seed Treatment, containing the active constituent penflufen, would not be likely to have an unintended effect that is harmful to animals, plants or things or the environment if used according to the product label instructions.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Summary

The submitted efficacy trials demonstrated that EverGol Prime Seed Treatment is efficacious and safe to use on wheat and barley seed at the label rates of 40 mL to 80 mL/100 kg of seed for control of cereal smuts (suppression only of soil-borne flag smut) and suppression of rhizoctonia root rot. The higher rate is recommended in situations conducive to greater risk of rhizoctonia root rot damage. There was no evidence of phytotoxicity or negative effects on crop establishment or vigour in any of the submitted trials. The probability of disease resistance arising from the use of the product is considered minimal because the seed treatment is limited to a single pre-planting application and the treatment is preventative by nature.

8.2 Efficacy

Suppression of rhizoctonia in wheat

Data from four Australian field trials conducted between 2007 and 2009 were submitted using wheat seed sown into soil either naturally infested or inoculated with *Rhizoctonia solani.* EverGol Prime Seed Treatment at 10, 15, 20 or 30 g ac/100 kg seed reduced the spear tipping on seminal roots and increased plant biomass by 50-51 days after planting (DAP) relative to the untreated controls. The 30 g ac/100 kg seed treatment gave suppression equivalent to the Dividend standard. These trials support the label claim that EverGol Prime Seed Treatment suppresses rhizoctonia in wheat when used at the rate of 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed).

Suppression of rhizoctonia in barley

Data from five Australian field trials conducted between 2008 and 2010 were submitted using barley seed sown into soil either naturally infested or inoculated with *Rhizoctonia solani.* EverGol Prime Seed Treatment at 10, 15, 20, 25, 30 or 40 g ac/100 kg seed reduced root infection, reduced the spear tipping of seminal roots, and increased plant biomass by 38--56 DAP relative to the untreated controls. The treatments gave suppression equivalent to the Dividend standard. These trials support the label claim that EverGol Prime Seed Treatment suppresses rhizoctonia in barley when used at the rate of 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed).

Control of common bunt (*Tilletia* species) in wheat

Five Australian trials were submitted that were conducted from 2004 – 2009 using wheat lines susceptible to bunt and inoculated with bunt spores prior to the seed treatments. Good infection levels developed in the trials in the untreated controls. EverGol Prime Seed Treatment at 5 to 20 g ac/100 kg seed gave 89-100% control. The industry standard treatments with Raxil and Dividend gave 100% control; the untreated controls had 3.6-38% uninfected. These trials support the label claim that EverGol Prime Seed Treatment controls common bunt in wheat when used at the rate of 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed).

Control of seed-borne flag smut (*Urocystis agropyri*) in wheat

Two Australian trials were submitted using seed pre-inoculated with flag smut spores. EverGol Prime Seed Treatment at 10, 15 or 20 g ac/100 kg seed gave 100% control. The industry standard treatments with Raxil and Dividend gave 100% control; the untreated controls had 7.8-8.3% uninfected. These trials support the label claim that EverGol Prime Seed Treatment controls seed-borne flag smut in wheat when used at the rate of 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed).

Suppression of soil-borne flag smut (*Urocystis agropyri*) in wheat

Two Australian trials were conducted in fields with wheat stubble that had a history of soil-borne flag smut. In the first trial, EverGol Prime Seed Treatment at 10 g ac/100 kg seed gave 87-90% control. In the second trial, the 15 and 20 g ac/100 kg seed treatments gave levels of control lower than the 10 g ac/100 kg seed treatment. The industry standard treatments with Raxil gave 100% control. These trials support the label claim that EverGol Prime Seed Treatment suppresses soil-borne flag smut in wheat when used at the rate of 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed) considering consistent total control was difficult to demonstrate in the field trials.

Control of loose smut (*Ustilago tritici*) in wheat

Four Australian trials were submitted using seed that had been retained from an infected crop. EverGol Prime Seed Treatment at 5, 10, 15 or 20 g ac/100 kg seed gave 69-100%, 93-100%, 100% and 100% control, respectively. The industry standard treatments with Raxil gave 94-100% control; the untreated controls had 0.19-0.35% uninfected. These trials support the label claim that EverGol Prime Seed Treatment controls loose smut in wheat when used at the rate of 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed).

Control of covered smut (*Ustilago segetum*) in barley

Four Australian trials were submitted using susceptible cultivars inoculated with spores prior to seed treatments to ensure infection. In all four trials, EverGol Prime Seed Treatment at 10, 15 or 20 g ac /100 kg seed gave 100% control of covered smut in barley compared to the untreated controls were there was 0.11-15% uninfected. These trials support the label claim that EverGol Prime Seed Treatment controls covered smut in barley when used at the rate of 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed).

Control of loose smut (*Ustilago nuda* var. *hordei*) in barley

Eight trials were submitted which demonstrated that EverGol Prime Seed Treatment used at the rate of 5 or 10 g ac /100 kg seed provided good control of covered smut with 100% control being achieved in most cases this was superior to that level of control achieved with the industry standard treatments. These trials support the label claim that EverGol Prime Seed Treatment at 40 to 80 mL/100 kg seed (9.6 to 19 g ac/100 kg seed) controls loose smut in barley.

8.3 Crop safety

Data presented from 12 trials supported the claim that EverGol Prime Seed Treatment applied as a seed treatment at rates up to 80mL/100 kg of seed is safe to use on cereals. There was no detrimental effect on plant establishment rates for either wheat or barley although an early improvement in wheat establishment was generally observed (10 to 20 DAP) this was not maintained to final establishment numbers (25 to 35 DAP) and plant stand was similar in EverGol Prime Seed Treatment treated and industry standard treatments such as Raxil. Similarly, for crop biomass assessments EverGol Prime Seed Treatment treated seed resulted in crop biomass data that was equivalent to that observed for the industry standard seed treatment.

8.4 Resistance management considerations

Penflufen is classified by FRAC as a group 7 active (succinate dehydrogenase inhibitors). Fungicides from this group pose a medium to high risk of disease resistance development. The probability of disease resistance arising from the use of the EverGol Prime Seed Treatment is considered minimal because the seed treatment is limited to a single pre-planting application and the treatment is preventative by nature. Rotational products with different modes of action are registered for most proposed uses.

8.5 Conclusions

In relation to its assessment of efficacy under section 14(3)(f), the APVMA is satisfied that EverGol Prime Seed Treatment, containing the active constituent penflufen, can be used safety and effectively if used according to the product label instructions.

9 LABELLING REQUIREMENTS

MAIN PANEL

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

EverGol® Prime

SEED TREATMENT

BAYER

ACTIVE CONSTITUENT: 240 g/L PENFLUFEN

GROUP	7	FUNGICIDE

For the suppression of rhizoctonia root rot and control or suppression of smut diseases of wheat and barley as specified in the DIRECTIONS FOR USE table

*** L**

(Label code)

* 5 L, 10 L

REAR PANEL

DIRECTIONS FOR USE

CROP	DISEASE	RATE	CRITICAL COMMENTS
Wheat	Bunt (*Tilletia* spp.) Flag smut (seed and soil-borne) (*Urocystis agropyri*) Loose smut (*Ustilago tritici*) Rhizoctonia root rot (*Rhizoctonia solani*)	40 to 80 mL/ 100 kg seed	EverGol® Prime is applied to seed prior to sowing. Ensure even coverage of seed. EverGol® Prime will suppress rhizoctonia root rot and its symptoms. Suppression of rhizoctonia root rot by EverGol® Prime is characterised by a reduction in root damage, an increase in root growth and an increase in above ground biomass. Use higher rates in situations conducive to greater risk of rhizoctonia root rot damage and/or higher yielding situations. EverGol® Prime will provide suppression of soil-borne flag smut.
Barley	Covered smut (*Ustilago segetum*) Loose smut (*Ustilago nuda* var. *hordei*) Rhizoctonia root rot (*Rhizoctonia solani*)		

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION

WITHHOLDING PERIODS

Harvest: NOT REQUIRED WHEN USED AS DIRECTED
Grazing: DO NOT GRAZE PLANTS GROWN FROM TREATED SEED, OR CUT FOR STOCK FOOD WITHIN 5 WEEKS OF SOWING

Fungicide Resistance Warning **GROUP 7 FUNGICIDE**

EverGol® Prime is a member of the carboxamide group of fungicides. For fungicide resistance management EverGol® Prime is a Group **7** fungicide. Some naturally occurring individual fungi resistant to EverGol® Prime and other Group **7** fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by this product and other Group **7** fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, Bayer CropScience Pty. Ltd. accepts no liability for any losses that result from failure of EverGol® Prime to control resistant fungi.

Application

EverGol® Prime Seed Treatment should be mixed with water to give even coverage of seed. The quantity of water used for mixing will vary depending on type of equipment and quality of seed. A guide to the volume of mixture required for even coverage is 400 - 600 mL (i.e. EverGol® Prime plus water) with each 100 kg of seed. Do not use more than 600 mL of mixture (product + water) with each 100 kg of seed.
Lower mixture rates can be used when the seed is treated professionally. The mixture should be gently stirred regularly. Only plant treated seed using equipment that buries seed in the soil.

REAR PANEL (continued)

Seed Quality
EverGol® Prime seed treatment should not be used on seed with more than 12% moisture content, or on sprung, sprouted, damaged or severely pinched seed, or seed of poor viability. If in doubt, have a germination test carried out on the seed before treatment to ensure that it is of acceptable standard. Treating with EverGol® Prime as directed will raise the moisture level of the seed by up to 0.6%, depending on weather conditions at treatment. The use of EverGol® Prime mixed with water at recommended rates will have no effect on the storage life of treated sound seed.

Storage of Treated Seed
For information on storing treated seed contact the Bayer CropScience Technical Enquiry Hotline 1800 804479 or your local Bayer CropScience representative.

Compatibility
For the latest compatibility recommendations contact the Bayer CropScience Technical Enquiry Hotline 1800 804479 or your local Bayer CropScience representative.

Labelling of Treated Seed
Label treated seed with the appropriate precautions using printed sacks, labels or bag tags.

Cleaning Up
Equipment should be thoroughly cleaned with water. In the event of changing from this water based flowable formulation to a solvent-based liquid formulation, it is essential to rinse equipment with methylated spirits after thoroughly cleaning with water. If changing from a solvent based liquid to this water based flowable, thoroughly clean with methylated spirits then rinse with water. Failure to do so will result in clogging of equipment.

PRECAUTION
Do not use treated seed for human or animal consumption. Do not allow seed treated with this product to contaminate seed intended for human or animal consumption. If possible, use a separate auger for treating seed. If using the same auger for treating seed and moving grain for human consumption, remove all EverGol® Prime residues from the auger to avoid contaminating untreated seed with seed treatment residues.

Re-handling
Do not allow re-handling of treated seed until dry unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF LIVESTOCK
Seed treated with this product must not be used for animal consumption or poultry feed or mixed with animal feed. DO NOT allow seed treated with this product to contaminate seed intended for animal consumption.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product, used containers or bags which have held treated seeds. DO NOT feed treated seed or otherwise expose to wild or domestic birds. Any spillages of treated seed, however minor, must be cleaned up immediately, preferably by recovery and re-use. If disposal is required, ensure treated seeds are thoroughly buried and not accessible to birds and other wildlife.

REAR PANEL (continued)

STORAGE AND DISPOSAL
Product and Original Container
Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight. Do not store near foodstuffs or animal feed.
Triple rinse containers before disposal. Add rinsings to slurry in auger/mixer, or dispose of rinsings according to State/Territory legislative requirements. DO NOT dispose of undiluted chemicals on site. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty containers or product. Do not re-use empty container for any other purpose.

Treated Seed and Containers of Treated Seed
When treated seed is stored it should be kept apart from other grain and the bags or containers should be clearly marked to indicate the contents have been treated with this product. DO NOT use treated seed for human consumption. Bags which have held treated seed are not to be used for any other purpose.

Application Equipment
Rinse all equipment with clean water immediately after use and dispose of rinsings according to State/Territory legislative requirements.

SAFETY DIRECTIONS
Avoid contact with eyes and skin. When preparing the product for use and using the product, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow length chemical resistant gloves and impervious foot wear. Wash hands after each use. After each day's use, wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone: Australia 13 11 26.

SAFETY DATA SHEET
Additional information is listed in the Safety Data Sheet, which can be obtained from www.bayercropscience.com.au.

EXCLUSION OF LIABILITY
This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Bayer CropScience Pty. Ltd. accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

APVMA Approval No.: 64744/49879

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FOR 24 HOUR SPECIALIST ADVICE
IN EMERGENCY ONLY
PHONE **1800 033 111**

BAR

DrumMuster Logo

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Technical Enquiries: 1800 804 479 (Label code)

Batch Number:
Date of Manufacture:

ABBREVIATIONS

ac	active constituent
ACCS	Department of Health and Ageing Advisory Committee on Chemical Scheduling
ADI	acceptable daily intake (for humans)
ARfD	acute reference dose
$AUC_{0-\infty}$	area under the curve
BBCH	Biologisch Bundesanstalt Bundessortenamt und Chemische Industrie scale for phonological development stages of a plant
bw	bodyweight
C_{max}	maximum plasma concentration
d	day(s)
DAP	days after planting
DT_{50}	Time taken for 50% of the concentration to dissipate
DT_{90}	Time taken for 90% of the concentration to dissipate
EC_{50}	concentration at which 50% of the test population are immobilised
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
F_1	first generation
F_2	second generation
FOB	functional observation battery
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GAP	good agricultural practice
GD	gestation day
GIT	gastro-intestinal tract
GSD	geometric standard deviation
h	hour(s)
ha	hectare(s)
hc	historical control

HDPE	high density polyethylene
HPLC-MS-MS	high pressure liquid chromatography *or* high performance liquid chromatography with tandem mass spectrometry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_d	adsorption constant
kg	kilogram(s)
K_{oc}	organic carbon adsorption constant
L	litre(s)
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOAEL	Lowest observable adverse effect level
LOQ	limit of quantitation – level at which residues can be quantified
LR_{50}	rate that kills 50% of the test population of organisms
mg	milligram(s)
mL	millilitre(s)
MMAD	mass median aerodynamic diameter
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MTD	maximum tolerated dose
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
NK	natural killer
NOAEL	lowest observable adverse effect level
NOEC	no observable effect concentration
NOEL	no observable effect level

NOHSC	National Occupational Health and Safety Commission
P_1	first parent generation
PBI	plant back interval
Pen-3HB	metabolite BYF 14182-3-hydroxy-butyl
Pen-D3C	metabolite BYF 14182-bis-desmethyl-3-carboxylic acid
Pen-HGT	metabolite BYF 14182-homoglutathione
Pen-PCX	metabolite BYF 14182-pyrazole-4-carboxamide
PPE	personal protective equipment
ppm	parts per million
SDH	succinate dehydrogenase
SWA	Safe Work Australia
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
t_{max}	time to maximum plasma concentration
TRR	total radioactive residue
µg	microgram(s)
WHO	World Health Organization

GLOSSARY

Acceptable daily intake	The daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk to the health of the consumer on the basis of all the known facts at the time. The ADI is expressed in milligrams of the chemical per kilogram of body weight per day (mg/kg/day). It is derived from the no-observed-effect level (NOEL) observed in the most sensitive animal species, utilising an appropriate safety factor.
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration. The ARfD is expressed as milligrams per kilogram of body weight.
Acute reference dose	The ARfD of a chemical is an estimate of the amount of a substance in food and/or drinking water, normally expressed on a body-weight basis, that can be ingested in a period of 24 hours or less, without appreciable risk to the consumer, on the basis of all known facts at the time of the evaluation.
Carcinogenicity	The ability to cause cancer
CAS registry	A database of the Chemical Abstracts Service (CAS) in which numbers are randomly assigned to compounds and are unique for each compound.
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Efficacy	Production of the desired effect
Evaluation	A written assessment of study reports or other data examined in the course of an appraisal by the APVMA for the granting or refusing of an application or other consideration
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Maximum residue limit	The maximum concentration of a chemical residue that is legally permitted in or on a food or feed commodity when that chemical is applied according to good agricultural practice (GAP) or good practice in the use of veterinary drugs (GPVD)
Metabolism	The chemical processes that maintain living organisms
New active constituent	An active constituent that has not previously been approved for use in an agricultural /veterinary chemical product in Australia
Photolysis	Breakdown of chemicals due to the action of light

Product	A formulation containing one or more active constituents, and possibly non-active constituent(s), which is intended for application, with or without dilution prior to use, and which is labelled with directions for use
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

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