Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active bicyclopyrone in the product Talinor Herbicide

APVMA Product Number [P82256]

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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, Department of Environment and Energy, Department of Agriculture and Water Resources, 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 application requirements and data 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 or animal safety.

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

Making a submission

In accordance with section 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether Talinor Herbicide should be registered. Submissions should relate only to matters that are required by the APVMA to be taken into consideration in determining whether the safety, efficacy or trade criteria have been met. Submissions should state the grounds on which they are based.

Submissions must be received by the APVMA by close of business on 1 May 2017 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:

Case Management and Administration Unit
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PO Box 6182
Kingston ACT 2604
Phone: +61 2 6210 4701
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

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] A full definition of 'confidential commercial information' is contained in the Agvet Code.

1 INTRODUCTION

1.1 Applicant

Syngenta Australia Pty Ltd

1.2 Purpose of application

Syngenta Australia Pty Ltd has applied to the APVMA for registration of the new product Talinor Herbicide containing 175 g/L bromoxynil present as the octanoate, 37.5 g/L bicyclopyrone and 9.4 g/L cloquintocet-mexyl in an emulsifiable concentrate (EC) formulation.

This publication provides a summary of the information reviewed and an outline of the regulatory considerations for the proposed registration of Talinor Herbicide, containing the new active constituent bicyclopyrone.

Bromoxynil present as the octanoate (herbicide) and cloquintocet-mexyl (crop safener) are APVMA approved active constituents which are present in other APVMA registered products.

Bicyclopyrone was assessed under a Global Joint Review (GJR) workshare arrangement where applications were submitted and considered concurrently in Australia, Canada and USA. The product Talinor Herbicide has been considered separately from the GJR workshare and is new to the Australian market. The active bicyclopyrone as well as the end-use product will be manufactured overseas and imported into Australia.

1.3 Product claims and use pattern

Talinor Herbicide is a selective herbicide. The proposed use pattern is as a foliar spray applied in a tank mix with the registered Adigor Spray Adjuvant (60114) for the early post-emergent control and suppression of broadleaf weeds in wheat (except durum wheat) and barley (between wheat and barley crop stages GS12 and GS32). The addition of cloquintocet-mexyl as an herbicide safener, is to reduce the effect of the herbicide on crop plants.

The product is to be applied by ground application equipment, at product rates between 500 and 1200 mL per hectare depending on the species and size of the target weeds. A range of rates may be used for certain uses and higher product rates are indicated where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rates should also be used when environmental conditions are marginal, such as low soil moisture.

1.4 Mode of action

Bicyclopyrone is a selective herbicide. It is a member of the triketone sub-group of the class of herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (4-HPPD). There are no herbicides of the triketone sub-group currently registered in Australia. For weed resistance management purposes bicyclopyrone is a Group H herbicide.

Bromoxynil-octanoate has the inhibition of photosynthesis at photosystem II mode of action. Bromoxynil is a member of the Group C herbicides, in the nitrile sub-group. Cloquintocet-mexyl is a crop safener, which accelerates the detoxification of herbicides in cereals and is not subject to a resistance management strategy.

For weed resistance management purposes Talinor Herbicide is a Group C, H herbicide.

1.5 Overseas registrations

An emulsifiable concentrate formulation containing 200 g/L bicyclopyrone is registered in the USA for uses in corn.

A ZC (combination of capsule suspension (CS) and suspension concentrate (SC)) formulation containing 7.1 g/L bicyclopyrone, 12.8 g/L benoxacor, 120 g/L atrazine, 28.5 g/L mesotrione and 257 g/L S-metolachlor is registered in the USA for use in corn and in Canada for use on corn and sweet corn.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

Bicyclopyrone is a solid at room temperature. It is weakly acidic (pKa of 3.06), and as a result becomes increasingly water soluble as the pH is increased and the acidic bicyclopyrone hydroxy group is deprotonated (the water solubility increases from 1.2 to 119 g/L as the pH is increased from 3 to 9.2). Bicyclopyrone is also highly soluble in polar organic solvents (acetone, dichloromethane, methanol, and ethyl acetate) and aromatic hydrocarbons (toluene) and moderately soluble in aliphatic hydrocarbons (hexane). As expected from the water solubility, bicyclopyrone has a low octanol-water partition coefficient, especially at higher pH. Bicyclopyrone is not explosive or flammable.

The APVMA has evaluated the chemistry (manufacturing process, quality control procedures, batch analysis, analytical methods, physico-chemical properties, and spectroscopic data) and toxicological aspects of the active constituent bicyclopyrone and found them to be acceptable. The active constituent was approved on 24 August 2016 under approval number 68271.

The active constituent will be imported into Australia both as the technical material for formulation into end use products in Australia, and as fully formulated product.

Details of the chemical name, structure, and physicochemical properties of bicyclopyrone are tabulated below.

Table 1: Nomenclature of bicyclopyrone

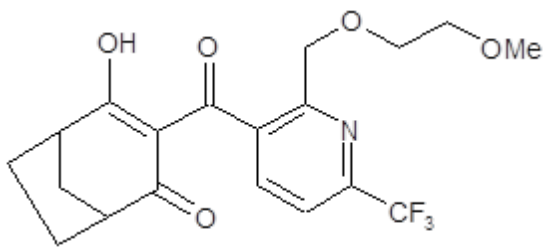
COMMON NAME (ISO):	Bicyclopyrone
IUPAC NAME:	4-Hydroxy-3-{2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridyl]carbonyl}bicyclo[3.2.1]oct-3-en-2-one,
CAS REGISTRY NUMBER:	352010-68-5
EMPIRICAL FORMULA:	C19H20F3NO5
MOLECULAR WEIGHT:	399.39 g/mol
STRUCTURAL FORMULA:	

Table 2: Physicochemical properties of bicyclopyrone

APPEARANCE:	White crystalline powder (pure substance, 99.9%); yellow-beige agglomerated powder (technical material, 96.7%)
MELTING POINT:	65.3°C (pure substance)
DENSITY:	1.503 at 20.5°C (pure substance)
WATER SOLUBILITY:	1.2 (pure water, a pH of about 3) 38 (pH 4.9) 119 (pH 7.2) 119 (pH 9.2) All in g/L, at 25°C (pure substance)
ORGANIC SOLVENT SOLUBILITY:	Acetone: > 500 Dichloromethane: > 500 Ethyl acetate: > 500 Hexane: 8.9 Methanol: > 500 Octanol: 91 Toluene: > 500 All in g/L, at 25°C, technical material
OCTANOL/WATER PARTITION COEFFICIENT (KOW):	0.25 (pH 5) -1.2 (pH 7) -1.9 (pH 9) All in log P_{ow}, at 25°C, pure substance
PKA	3.06 (20°C)
PH	2.9 (1.0% w/v solution, technical material)
VAPOUR PRESSURE AT 25OC:	< 5 x 10^{-6} Pa
SAFETY PROPERTIES:	Not classified as flammable, no ignition below the melting point, not explosive

On the basis of the data provided, and the toxicological assessment, the following APVMA Active Constituent Standard has been established for bicyclopyrone active constituent:

CONSTITUENT	SPECIFICATION
Bicyclopyrone	950 g/kg minimum (dry weight basis)

2.2 Formulated product

The product Talinor Herbicide will be formulated in Australia and overseas. Talinor Herbicide is an emulsifiable concentrate (EC) formulation containing the new active constituent bicyclopyrone, together with two existing active constituents, the herbicide bromoxynil (present as the octanoate ester) and the herbicide safener cloquintocet-mexyl. The product will be packaged in high density polyethylene (HDPE) and polyethylene terephthalate (PET) containers ranging in size from 5 to 1000 L. Suitable details of the product formulation, specifications for the ingredients, formulation process and quality control, product specifications, stability data for the product when stored in the proposed packaging, analytical methods for the active constituents in the product, and details of the packaging, were provided and evaluated.

Based on the assessment the APVMA is satisfied that the product will remain stable when stored for up to 2 years under normal conditions in the proposed commercial packaging.

Table 3 Identification of the proposed product

DISTINGUISHING NAME:	Talinor Herbicide
FORMULATION TYPE:	Emulsifiable Concentrate (EC)
ACTIVE CONSTITUENT CONCENTRATIONS:	Bicyclopyrone (37.5 g/L) Bromoxynil, present as bromoxynil octanoate (175 g/L) Cloquintocet-mexyl (9.4 g/L)

Table 4: Physicochemical properties of Talinor Herbicide

COLOUR:	Amber
ODOUR:	Aromatic
PHYSICAL STATE:	Liquid
APPEARANCE:	Clear
PH VALUE:	3.9 (1 % in deionized water)
ACIDITY:	0.29%
DENSITY:	1.101 g/cm^3 at 20ºC
SURFACE TENSION:	34.7 mN/m (6% w/v dilution)
VISCOSITY:	11.1mPa.s
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	Not oxidising
FLAMMABILITY:	Not flammable
PACK SIZES:	5–1000 L
PACKAGING MATERIAL:	HDPE and PET
PRODUCT STABILITY:	The product should remain within specifications for at least 2 years under normal conditions in HDPE and PET packaging

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, the registration of Talinor Herbicide is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

The toxicological database for bicyclopyrone, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of bicyclopyrone 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 exposures. 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.

The toxicology assessment of bicyclopyrone was conducted as part of a Global Joint Review (GJR) by scientists from the United States Environmental Protection Agency (US EPA), Health Canada Pest Management Regulatory Agency (PMRA) and the Office of Chemical Safety (OCS) within the Australian Department of Health. The US EPA was the primary reviewer for all the toxicity studies, and the PMRA and OCS were secondary reviewers. Australian independent toxicology assessments have used the terms of no observed effect level (NOEL) and lowest observed effect level (LOEL). However, since this report relies significantly on the international work share assessment, the OCS adopted the no observed adverse effect level (NOAEL) and low observed adverse effect level (LOAEL) approach using scientific justification for their adoption

Chemical class

Bicyclopyrone is a member of the 4-hydroxyphenyl pyruvate dioxygenase (HPPD)-inhibitor class of herbicides and belongs to the triketone chemical subclass.

Toxicokinetics and metabolism

In the rat, bicyclopyrone was rapidly absorbed with maximum plasma concentrations (Cmax) reached within 1–3 hours after oral dosing indicating rapid absorption into the systemic circulation. Means of 83% and 87% of the low dose were absorbed after 48 hours by males and females respectively. Means of 86% and 90% of the high dose were absorbed after 48 hours by males and females, respectively.

Renal elimination represented the principal route of excretion of radioactivity independent of sex or dose level, with the majority of the dose being excreted in urine within the first 24 hours following single oral administration. Faecal elimination accounted for 27% and 5% of the low dose in males and females respectively, with corresponding values of 23% and 6% of the high dose in males and females respectively. Biliary elimination accounted for 16% and 2% of the low dose in males and females, with corresponding values of 19% and 7% of the high dose in males and females respectively. Overall, these data indicate rapid

and almost complete absorption of bicyclopyrone, with the majority of the administered dose excreted in the first 24 hours.

Bicyclopyrone was poorly distributed in tissues with the highest tissue concentrations found in the liver and kidney, accounting for 4% and 0.3% of the dose in males respectively and 3% and 0.4% in females respectively with the low dose. The major component found in the liver was parent compound. The concentration of radioactive residues in the tissues seven days after administration was very low for both dose levels. A repeat oral dose study provided no evidence of accumulation in any of the tissues examined following administration of the low dose to rats for 28 consecutive days.

Bicyclopyrone was not extensively metabolised in the rat with unchanged parent compound being the principal radioactive component independent of dose or route (oral and IV).

Percutaneous absorption

Percutaneous absorption of bicyclopyrone was evaluated on the basis of a so-called ‘Triple pack’ approach, i.e., an in vivo study on rats was corrected by the ratio in permeability between human and rat skin in vitro to give a reliable estimate for dermal absorption in humans in vivo. In both studies, the test material was the proposed product, a soluble concentrate (SL) containing 200 g/L bicyclopyrone that was applied as a concentrate and as a 1:100 and 1/400 spray dilution.

Based on dermal absorption studies evaluated, for risk assessment purposes a calculated human dermal absorption factor of 0.04% was used for the concentrated formulation and a dermal absorption factor of 1.67% was used for the spray formulation.

Acute toxicity

Bicyclopyrone has low acute oral (LD50 > 5000 mg/kg bw, no deaths), dermal (LD50 > 5000 mg/kg bw, no deaths) and inhalational toxicity in rats (4-h LC50 > 5.2 mg/L, no deaths). It was a slight eye irritant but not a skin irritant in rabbits. Bicyclopyrone was not a skin sensitiser in the local lymph node assay in mice.

Systemic toxicity and mode of action (MoA)

In the dog the primary effect following oral administration of bicyclopyrone was an increase in plasma tyrosine levels in the 28–day and 52–week studies for which levels were measured. Similarly, in the rat, increased plasma tyrosine levels were seen in the 14–day and 28–day MoA oral studies for which tyrosine was measured. Tyrosine levels not being measured in the mouse or rat studies. The available sub-chronic and chronic oral studies in rats, mice and dogs indicate that the rat is the most sensitive species and the mouse was least sensitive to bicyclopyrone induced systemic toxicity. A NOAEL of 0.28/0.35 mg/kg bw/d (5 ppm in the diet) was identified in the chronic oral study in rats.

In rats, chronic oral administration of bicyclopyrone resulted in increased kidney weight, chronic progressive nephropathy (males only) and urine clinical chemistry changes as well as thyroid follicular hypertrophy (males only) and corneal opacity and corneal damage (neovascularisation), with decreased body weight and body weight gain seen at higher dose levels. Corneal opacity was also seen following chronic oral administration of bicyclopyrone in male and female dogs but not in male and female mice. In a short-term dermal study in rats, eye lesions (keratitis or degeneration of corneal epithelium) were seen in males at 250 mg/kg bw/d and greater.

However, it is widely accepted that markedly elevated tyrosine in rats is a direct consequence of HPPD inhibition; therefore, the ocular effects observed following exposure to HPPD inhibitors is due to elevated tyrosine. The observed increased incidences of corneal keratitis and regenerative hyperplasia in rats following chronic exposure to bicyclopyrone are not dose-related but parallel the increases in tyrosine, which are maximal at dietary concentrations of ≥ 500 ppm. Additionally, it has been noted previously with another HPPD inhibiting herbicide evaluated by OCS that mice tended to be less susceptible to the toxicity of the herbicide, with a lack of ocular effects up to the limit dose of 1000 mg/kg bw/d and rats are more susceptible. This is consistent with what has been seen for bicyclopyrone.

Additionally, a review of the literature revealed that evidence from human cases of hereditary diseases that affect tyrosine metabolism indicates that corneal opacity is observed in human with plasma tyrosine concentration of approximately 3000 nmol/mL. This can be considered to be the threshold of plasma tyrosine concentration for ocular effects in humans and in the event of complete inhibition of HPPD, this threshold is unlikely to be exceeded in humans. Furthermore, given the low dermal absorption rate of bicyclopyrone which is the main route of exposure to workers, systemic exposure occurring during occupational use is not expected to reach the threshold of 3000 nmol/mL (ie ocular findings are considered qualitatively but not quantitatively relevant to humans).

Additionally, it has also been reported in the literature that in contrast to ocular lesions seen in humans with tyrosinaemia type II (OMIM 276600), who have a deficiency in the enzyme tyrosine aminotransferase, and high tyrosine levels. In contrast, exposure of humans with tyrosinaemia type I (OMIM 276700), who have a deficiency in the enzyme fumarylacetoacetate hydrolase, to the pharmaceutical compound nitisinone (NTBC) which is a complete HPPD inhibitor does not result in the same marked elevation in tyrosine levels and does not cause ocular toxicity similar to that seen in the rat. While under treatment for tyrosinaemia type I dietary restriction to prevent significant tyrosine elevation is recommended, NTBC has also been used in clinical trials for alkaptonuria, another metabolic defect in the tyrosine catabolic pathway, without any dietary restriction and 1/40 patients developed corneal opacity which was reversed following discontinuation of treatment. Therefore, there is evidence that although humans can develop ocular lesions when tyrosine levels are highly elevated for prolonged periods of time, as is the case in tyrosinaemia type II, the administration of HPPD inhibitors, at doses which are intended to completely inhibit the HPPD enzyme rarely elevates tyrosine sufficiently to cause ocular lesions. Thus, in contrast to rats there is a substantially reduced risk of adverse ocular effects occurring in humans following exposure to HPPD inhibitors.

In male rats only, there was a treatment related increase in thyroid focal cell hypertrophy after 52 week of dietary administration of bicyclopyrone at a dose levels of 28.8 mg/kg bw/d and greater, and after 104 weeks of treatment this finding was also associated with thyroid follicular hyperplasia at the same dose levels. The potential MoA for the observed histopathological thyroid changes in male rats was investigated. It was demonstrated that bicyclopyrone was not an inhibitor of rat thyroid peroxidase activity in vitro. The effect of bicyclopyrone on liver and thyroid function was also determined in rats in vivo where it was demonstrated that dietary treatment of male rats with bicyclopyrone results in increased tyrosine, decreased T3 and T4 (thyroxine), increased thyroid follicular cell hypertrophy and increased liver weight associated with increased hepatocellular centrilobular hypertrophy and increased hepatic UDPGT activity. Thus, there was evidence that bicyclopyrone effected thyroid hormone homeostasis.

Furthermore, due to known species differences in thyroid function, due to the plasma half-life of T4 being shorter in rodents (12–24 hours) than in humans (5–9 days), there is serum T4 binding with thyroxine-binding globulin in humans which is absent in rodents (meaning there is more unbound T4 in rodents susceptible to conjugation and biliary excretion), and constitutive TSH levels are significantly greater in rodents compared to humans (e.g. nearly 25 times greater in rats), rats are considered more susceptible to such thyroid hormone disturbances than humans. In support of this, it is reported in the scientific literature that in the rat free tyrosine can create conditions in the thyroid analogous to mild iodine deficiency, while the HPPD inhibitor NTBC has been used for the treatment of type I tyrosinaemia since 1991, with some patients therefore taking the drug for >20 years, and during this time there have been no reports of effects on thyroid function. Thus, it is clear that humans are significantly less sensitive than rats to elevated tyrosine levels due to HPPD inhibition and associated thyroid hormone disturbances that can lead to histopathological changes in the thyroid. Thus, the observed thyroid findings in rats following administration of bicyclopyrone are considered qualitatively but not quantitatively relevant to humans.

Genotoxicity and carcinogenicity

Bicyclopyrone did not exhibit any mutagenic potential in vitro in bacteria and mammalian cells with and without metabolic activation, and was not clastogenic in mammalian cells in vitro with and without metabolic activation. Similarly, bicyclopyrone was not clastogenic in rat bone marrow cells in vivo, and did not induce DNA repair, indicative of DNA damage, in rat liver cells in vivo.

In an 80 week carcinogenicity study in mice, an increased incidence of bronchiole-alveolar adenoma in the lung was observed at 940 mg/kg bw/d in males only. However, this incidence of this benign tumour was only slightly outside of the laboratory historical control range for this strain of mouse (36%, HC 24–30%), was seen in the absence of treatment related non-neoplastic change in the lung and the observed incidence of broncho-alveolar carcinoma was within the laboratory historical control range. Additionally, in males at 7000 ppm the maximum tolerated dose (MTD) was exceeded as shown by body weight gain being decreased for the duration of the study (↓13% to↓29%). It is also noted that the laboratory historical control range was based on a relatively small number of studies. No increased incidence of tumour findings was seen in female mice.

Consequently, it is considered that the slight increase in these benign lung tumours only above the laboratory historical control range in one sex at a high dose level also exceeding the MTD do not provide robust and reliable evidence of a carcinogenic potential.

In the 104–week carcinogenicity phase of a dietary study in male rats, at 500, 2500 and 5000 ppm (equivalent to 0.28, 141 and 280 mg/kg bw/d) a slight increase was seen in squamous cell papilloma of the cornea was seen in 2 males (4% animals) at each dose level along with squamous cell carcinoma of the cornea in 1, 1 and 3 males (2%, 2% and 6% of animals) respectively that was not statistically significant but was absent in control animals. These findings were seen in the presence of ocular opacity, keratitis and regenerative hyperplasia of the cornea, and as discussed above under 'Systemic toxicity and mode of action', rats are significantly more sensitive to the effects of HPPD inhibitors than humans, and that the ocular keratitis and regenerative hyperplasia observed in rats is directly linked to the resulting highly elevated plasma tyrosine. Furthermore, the progression of ocular keratitis and regenerative hyperplasia in the rat cornea to corneal cell tumours at high levels of tyrosine, while not directly demonstrated, may further suggest a role of tyrosine and not bicyclopyrone in the development of these tumours. Consequently, overall, it is considered that the observed low incidences of corneal cell tumours in male rats only are unlikely to be relevant to humans. No increased incidence of tumour findings was seen in female rats.

Reproductive and developmental toxicity

In a 2–generation dietary study in rats, whose dose levels were determined from a multi-generation dose range-finding study, parental toxicity was seen from 25 ppm (2.15 and 2.65 mg/kg bw/d in males and females) and consisted of ocular effects including corneal opacity and vascular keratitis in F0 and F1 males, as well as an increased incidence of pelvic dilation of the kidney in F0 and F1 males and in F1 females. Decreases in body weight and body weight gain were also seen at higher dose levels. Additionally, in F1 males there was a significant increase in the number of abnormal sperm and a decrease in sperm velocities at a dose of 5000 ppm (436 mg/kg bw/d), though no treatment related effect was seen on reproduction. Consequently, this singular finding, also seen in the presence of general toxicity (e.g. decreased body weight), is not considered to demonstrate a reproductive toxicity potential for bicyclopyrone. Similar to parental animals, ocular effects (corneal opacity, corneal roughness and vascular keratitis) were seen in F1 and F2 animals, along with decreased bodyweight and bodyweight gain in the F1 generation, though from 500 ppm (43.65 and 52.7 mg/kg bw/d in males and females).

Oral (gavage) developmental toxicity studies on bicyclopyrone were performed in Wistar rats and in two strains of rabbit, the New Zealand White (NZW) and Himalayan, whose dose levels were determined from developmental dose-range finding studies.

In rats, skeletal variations (increased incidence of full or rudimentary supernumerary ribs, pelvic girdle malposition and long costal cartilage 11) were observed in the presence of maternal toxicity at doses of 100 mg/kg bw/d, the lowest dose tested (i.e. a maternal and developmental LOAEL were not established). The skeletal variations while treatment related were considered a secondary non-specific consequence of the observed marked maternal toxicity (i.e. substantial decreases in body weight gain). Thus, bicyclopyrone was not considered to be a developmental toxicant in rats.

In New Zealand White rabbits, evidence of foetal toxicity included an increased incidence of two skeletal variations (13th full rib, 27th pre-sacral vertebrae) in the absence of maternal toxicity at 10 mg/kg bw/d. While these increases in the 13th full rib and 27th pre-sacral vertebrae were outside of the upper laboratory historical control range and are treatment related OCS considers that the change in the incidence of these two common variants alone do not warrant classification as a hazard for developmental toxicity. Furthermore, it was noted that no additional skeletal findings, or visceral findings, were seen at increased dose levels in the presence of severe maternal toxicity (i.e. at a dose level producing mortality/moribund status in does). Thus, bicyclopyrone was not considered to be a developmental toxicant in NZW rabbits.

Two studies were available in Himalayan rabbits, one with dose levels of 0, 10, 50 and 250 mg/kg bw/d (study 1) and the other with dose levels of 0, 1, 10 and 250 mg/kg bw/d (study 2). OCS considered the findings from both studies together, so as to allow a more informed view of potential spontaneous rates in foetuses and a more comprehensive dose response for maternal and foetal findings to be established.

In study 1, the maternal NOAEL was established at 50 mg/kg bw/d based on macroscopic findings in the stomach wall of females and a sustained absence in body weight gain from GD 7–13 at 250 mg/kg bw/day the highest dose tested. At 10 mg/kg bw/d the lowest dose tested, and in the absence of maternal toxicity, an increased incidence was seen in urogenital malformations (in 2% of foetuses, 14% of litters) that were absent in control animals from both studies along with skeletal variations. Also in the absence of maternal toxicity, at 50 mg/kg bw/d a treatment related and toxicologically significant increase was seen in septal variations of the heart (in 20% foetuses and 53% litters, with a highest incidence of 16% and 68% respectively seen in study 2) and in post-implantation loss (20.3% of implantation sites with a mean of per litter of 1.4, compared to upper historical control values of 15.9% and 1.2 respectively).

In study 2, the maternal NOAEL was established at 10 mg/kg bw/d based on two mortalities and signs clinical signs of toxicity along with signs of stomach irritation in two does at 250 mg/kg/d. At 10 mg/kg bw/d in the absence of maternal toxicity, and consistent with the findings in study 1 at the same dose level, urogenital malformation were seen (in 2% of foetuses and 5% of litters) along with skeletal variations.

Therefore, taking the findings from the two developmental studies in Himalayan rabbits together, it is considered that urogenital malformations were seen from 10 mg/kg/day along with skeletal variations, septal variations of the heart and post-implantation loss from 50 mg/kg/day, and septal defects of the heart (i.e. deverticula or abnormal appearance of the septal wall) at 250 mg/kg/day in this study. Maternal toxicity was seen from 50 mg/kg bw/d, so the urogenital malformations and skeletal findings at 10 mg/kg bw/d were seen in the absence of maternal toxicity, while OCS considers that the observed septal variations and defects along with post-implantation loss seen in the presence of maternal toxicity were unlikely to be a secondary non-specific consequence of such (i.e. are considered evidence of a developmental toxicity potential). Thus, bicyclopyrone was considered to be a developmental toxicant in Himalayan rabbits.

Neurotoxicity

No adverse effects were seen in an acute oral (gavage) neurotoxicity study in male and female rats at doses up to and including 2000 mg/kg bw.

In a subchronic dietary neurotoxicity study in rats, a decrease was seen in mean brain weight in males at 20, 500 and 5000 ppm (equivalent to 4, 35 and 336 mg/kg bw/d). However, the mean brain weight in male controls (2.38 g) was high compared to the historical control means (means of 2.2 g and 2.0 g for studies with 8 untreated males each), and with the exception of 1 male in the 500 ppm dose group all brain weights in males at 50 and 500 ppm were within the historical control range (1.96–2.29 g). Consequently, the statistical significant finding at 50 and 500 ppm of decreased brain weights in males only (both 8%, no evidence of a dose response) are considered incidental and not treatment related. While at 5000 ppm, the brain weight in only 2 of the 5 males was lower than the minimum historical control value. Furthermore, it is noted that this increase in mean brain weight in one sex was seen in the absence of an effect on functional parameters or histopathological changes to the brain. Additionally, no other studies have provided evidence of an adverse neurotoxic potential. Consequently, bicyclopyrone was not considered to be a neurotoxicant.

Immunotoxicity

Bicyclopyrone was not immunotoxic in female mice in a short term dietary study at doses up to and including 1192 mg/kg bw/d.

Product toxicity

The Talinor Herbicide formulation was demonstrated to be of low acute oral (550 mg/kg bw < LD_{50} < 1750 mg/kg bw, estimated at LD_{50} 1030 mg/kg bw), dermal (LD_{50} > 5000 mg/kg bw) and inhalational toxicity (LC_{50} > 5110 mg/m^3) in rats. The formulation was also a slight skin (rabbits) and slight eye irritant (rabbits), and a strong skin sensitiser (mouse LLNA).

3.2 Public health standards

Poisons scheduling

On the 19th November 2015 the delegate to the Secretary of the Department of Health published the final scheduling decision to create a new Schedule 6 listing for bicyclopyrone in the Standard for the Uniform Scheduling of Medicines and Poisons, with a cut-off to Schedule 5 in preparations at 20% or less of bicyclopyrone, along with an implementation date of 1 February 2016.

Talinor Herbicide contains 3.75% of bicyclopyrone which is listed in Schedule 5 of the SUSMP.

Bromoxynil is listed in Schedule 6 of the SUSMP with no cut-offs or exemptions.

Cloquintocet-mexyl is listed in Schedule 5 of the SUSMP with no cut-offs or exemptions.

Talinor Herbicide contains >25% Liquid Hydrocarbons which are listed in Schedule 5 of the SUSMP.

Talinor Herbicide is therefore classified as a Schedule 6 poison. Based on the acute toxicity profile of the product and the concentrations of the active constituents and solvent, this classification is considered appropriate.

No observable Effect Level (NOEL)/Acceptable Daily Intake (ADI) /Acute reference Dose (ARfD)

The acceptable daily intake (ADI) for humans is level of intake of an agricultural or veterinary chemical which can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL/NOAEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety (uncertainty) factor. The magnitude of the safety (uncertainty) factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The toxicological database for bicyclopyrone 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 effects of bicyclopyrone identified in oral studies was ocular toxicity in rats and dogs, decreased body weight, body weight gain and food consumption in male rats, increased kidney weight, changes in urine clinical chemistry, and thyroid follicular hyperplasia in rats and urogenital malformations, skeletal variations, septal variations and defects, and post-implantation loss in rabbits.

The most sensitive NOAEL to establish an ADI is 0.28 mg/kg bw/d from a 52 week chronic/104 week carcinogenicity study in rats based on increased kidney weight, chronic progressive nephropathy and thyroid follicular hyperplasia in males, and changes in urine clinical chemistry (increased urine specific gravity, protein and ketones), corneal opacity and corneal damage in both sexes at doses of 25.8 mg/kg/day.

However, it is noted that in developmental studies in Himalayan rabbits, urogenital malformations along with skeletal variations were seen at 10 mg/kg bw/d with a NOAEL of 1 mg/kg bw/d established for these findings. Noting that lack of information on similarities between humans and rabbits in tyrosine kinetics, the available data presents a concern that children and infants may be susceptible to these visceral and skeletal effects, and this concern justifies the use of an additional safety factor. However, noting that no such findings were seen in NZW rabbits (or Wistar rats) suggesting that Himalayan rabbits may be uniquely sensitive to bicyclopyrone induced foetal toxicity, the relatively low incidence of urogenital malformations (2% equating to 2/129 foetuses in one study and 2/114 in another) and that the skeletal variations are considered minor and unlikely to have serious implication for growth and development in humans, a 300–fold safety factor is proposed, consisting of safety actors of 100 for potential intraspecies and interspecies variation, and a safety factor of 3 intended for the further protection of children, infants and potential prenatal toxicity.

The ADI for bicyclopyrone is therefore established at 0.001 mg/kg bw/d (rounded up) using the NOAEL of 0.28 mg/kg bw/d from a dietary 52 week chronic/104 week carcinogenicity study in rats and applying a 300– fold safety factor.

The ADI for bromoxynil is 0.003 mg/kg bw/d, established in 1993 based on a NOEL of 0.3 mg/kg bw/d from a 1–year dog dietary study based on biochemical changes and increased liver weights at the next highest dose of 1.5 mg/kg bw/d. The application of a safety (uncertainty) factor of 100 was used for intraspecies variability and interspecies differences.

The ADI for cloquintocet-mexyl is 0.04 mg/kg bw/day based on a NOEL of 4.3 mg/kg bw/day for thyroid follicular epithelium hyperplasia in females at 41.3 mg/kg bw/day and above in a 2–year rat study and using a 100 fold safety (uncertainty) factor. The ADI was established in 1994.

The acute reference dose (ARfD) is the estimate of the amount of an agricultural or veterinary chemical in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in 1 meal or during 1 day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

For setting an ARfD, the most appropriate study to use is a Himalayan rabbit developmental study. In this study, urogenital malformations along with skeletal variations were seen at 10 mg/kg bw/d with a NOAEL of 1 mg/kg bw/d established for these findings.

The ARfD for bicyclopyrone is therefore established at 0.01 mg/kg bw using the NOAEL of 1 mg/kg bw/d in an oral developmental study in Himalayan rabbits and applying a 100-fold safety (uncertainty) factor. In regard to the ARfD it should be noted that the ARfD for bicyclopyrone applies only to women of child-bearing age. An ARfD for the population as a whole is not considered to be necessary.

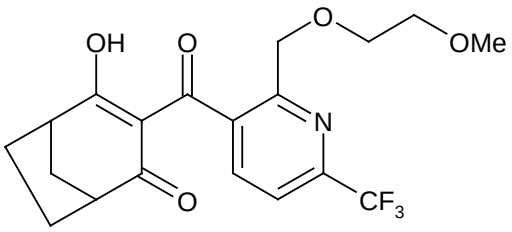
No ARfD has been established for bromoxynil or cloquintocet-mexyl and no data were submitted to enable an ARfD to be set.

4 RESIDUES ASSESSMENT

4.1 Introduction

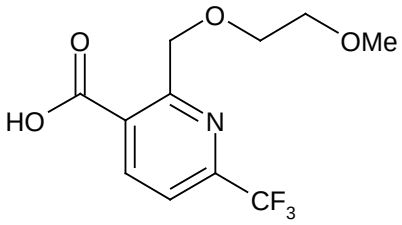
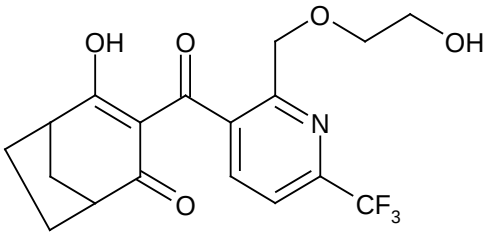
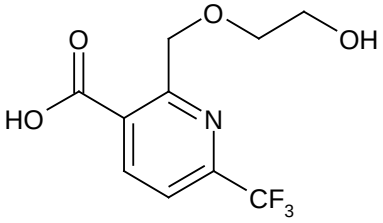
Talinor Herbicide contains the new active constituent bicyclopyrone and the approved active constituents bromoxynil and cloquintocet-mexyl, and is proposed for use on wheat and barley. As the proposed use of Talinor Herbicide (37.5 g/L bicyclopyrone + 175 g/L bromoxynil as the octanoate + 9.4 g/L cloquintocet-mexyl) is at the same or lower levels compared to registered uses of bromoxynil octanoate and cloquintocet-mexyl, no further discussion of the proposed use of bromoxynil octanoate and cloquintocet-mexyl on wheat and barley is considered necessary.

As part of the residues assessment of bicyclopyrone, plant and animal metabolism studies, supervised residue trials, analytical methodology, fate in storage and processing data and residues in trade information were considered.



Bicyclopyrone

The following relevant compounds are also referred to in the following discussion.

Code	Chemical Structure
SYN503780	
CSAA915194	
CSCD686480	

4.2 Metabolism

Plants

Metabolism studies were conducted in corn and sugarcane with [bicyclooctenone-6,7-14C2]- or [pyridine-3-14C]-bicyclopyrone. Bicyclopyrone was extensively metabolised in both crops. Parent bicyclopyrone was found in corn forage and was absent in all other samples examined. A number of major metabolites were formed by hydroxylation on one or two sites on the bicyclic ring, and/or desmethylation and hydroxylation of the methoxyethoxymethyl side chain. Some conjugation to glycosides was observed with the hydroxyl derivatives.

In the confined rotational crop study [bicyclooctenone-6, 7-14C2]- or [pyridine-3-14C]-bicyclopyrone were applied as a single spray application to separate containers of bare soil at nominal rates of 200 and 350 g ai/ha. Following rotational intervals of 30, 60, 120, 180 and/or 270 days after application, spring wheat, turnip, and/or spinach were sown into the soil and grown to crop maturity. The uptake of radioactive residues was greatest in rotated wheat commodities. Analysis of wheat commodities showed minor residues of bicyclopyrone (≤ 5.8% TRR; ≤ 0.026 mg/kg). Bicyclopyrone is extensively metabolised in rotational wheat to a complex mixture of components. The principal residues identified were also found in the bicyclopyrone corn and sugarcane primary crop metabolism studies.

Livestock

Livestock metabolism studies were conducted with repeated oral administration of [bicyclooctenone-6,7-14C2]- or [pyridine-3-14C]-bicyclopyrone and to lactating goats and hens.

The hen metabolism study in which radiolabelled bicyclopyrone was administered at 24.1 ppm (pyridinyl label) or 22.0 ppm (bicyclooctenone label), showed that bicyclopyrone was metabolised minimally and was the largest component of the total radioactive residues in all hen commodities. Observed residue levels for bicyclopyrone ranged from 1.51 mg/kg (86.4% TRR) in liver, to 0.07 mg/kg (83.5% TRR) in muscle.

The lactating goat metabolism study in which radiolabelled bicyclopyrone was administered at 33.8 ppm (pyridinyl label) or 34.3 ppm (bicyclooctenone label) showed that the principal metabolites observed were CSAA915194 and unchanged bicyclopyrone which were found in all goat commodities. The largest levels of each occurred in liver and kidney at 1.92 mg/kg (70.4% TRR) and 0.66 mg/kg (50.2% TRR) respectively for CSAA915194 and 0.436 mg/kg (16.0% TRR) and 0.572 mg/kg (43.5% TRR) respectively for bicyclopyrone.

4.3 Analytical methods

A number of relevant analytical methods are available which have been validated for parent bicyclopyrone and metabolite SYN503780 in plant commodities.

Details were also submitted of common moiety methods for the determination of bicyclopyrone and CAA915194 and structurally related metabolites (as SYN503780 and CSCD686480) in both plant and animal matrices. Therefore residues which are structurally similar to bicyclopyrone, as well as unchanged bicyclopyrone, will be included in the results. It is considered that the LOQ of the analytes in the common moiety methods is 0.02 mg/kg, when combined and expressed as parent bicyclopyrone. Recoveries using these methods were within acceptable limits.

4.4 Stability of the pesticides in stored analytical samples

Residues of bicyclopyrone and its metabolite SYN503780 have been shown to be stable in corn grain, wheat straw, spinach leaf, soybeans, lentils seeds, citrus (lemon fruit) and potato tubers when stored deep frozen at ≤-20±5°C for at least 24 months.

In the Australian residue trials submitted with the present application, all samples were maintained under freezer conditions prior to analysis and tested within 8 months of collection. Storage stability experiments were conducted on barley and wheat forage, grain and straw samples. Homogenised untreated specimens upon receipt at the laboratory (earliest received samples per crop) were fortified with known levels of bicyclopyrone and CSAA915194 an individual analytes. Residues analyses of the fortified samples, as per the analytical method (measurement of SYN503780 and CSCD686480 and conversion to residues of bicyclopyrone and CSAA915194) showed that bicyclopyrone residues were stable within the barley and wheat matrices over the storage duration from fortification to analysis.

4.5 Residue definition

Based on the available metabolism, residue trial and analytical methodology information, a suitable residue definition for bicyclopyrone in plant commodities is considered to be 'Bicyclopyrone and its structurally related metabolites determined as SYN503780 and CSCD686480 by a common moiety method and expressed as bicyclopyrone'.

On the basis that the goat and hen metabolism studies and the dairy cow feeding study indicate that it is likely that residues of bicyclopyrone and structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 will be present in liver and kidney from the consumption of animal feeds containing quantifiable residues, a suitable residue definition for bicyclopyrone in animal commodities is considered to be "Bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 and expressed as bicyclopyrone".

4.6 Residue trials

The proposed application rate for bicyclopyrone on barley and wheat is at a maximum of 45 g bicyclopyrone/ ha between growth stages 12 to 32, with a harvest WHP of 'Not required when used as directed' and a grazing WHP of 'DO NOT graze or cut for stock feed for 6 weeks after application'.

Residue trials in wheat (n=10) and barley (n=6) conducted in Australia in 2014 involved one application at 36–42 g ai/ha made at GS 32 - 37. Residues in grain at commercial harvest were <0.01 (6) mg/kg in barley and <0.01 (8) and 0.011 (2) mg/kg fin wheat.

MRLs of 0.02 mg/kg are recommended for bicyclopyrone on GC 0640 Barley and GC 0654 Wheat.

A processing study conducted in the US found bicyclopyrone residues to concentrate during processing to wheat bran by a mean/ median processing factor of 2.3×. Based on the highest residues (HR) in wheat grain (0.011 mg/kg), the highest predicted residue value (HR-P) in wheat bran is 0.025 mg/kg.

An MRL of 0.05 mg/kg is recommended for bicyclopyrone on CM 0654 Wheat bran, unprocessed.

The combined Australian dataset suitable for MRL estimation of residues in barley and wheat straw on a dry weight basis at harvest after one application at an application rate of 36 – 42 g a.i./ ha, and conversion to expected residues at an application rate of 45 g a.i./ha, is in rank order: 0.020, 0.028 (2), 0.032, 0.037, 0.041, 0.055, 0.058, 0.059, 0.060, 0.072, 0.080, 0.082, 0.092 and 0.10 (2) mg/kg (n = 16, STMR = 0.0585 mg/kg).

An MRL of 0.2 mg/kg is recommended for bicyclopyrone on AS 0081 Straw and fodder (dry) of cereal grains.

The combined Australian dataset suitable for MRL estimation of residues in barley and wheat forage on a dry weight basis 6 weeks after one application at an application rate of 36.0-41.6 g a.i./ ha), and conversion to expected residues at an application rate of 45 g a.i./ha, is in rank order: 0.047, 0.063, 0.067, 0.086, 0.12, 0.13 (2) and 0.30 mg/kg (n = 8, STMR = 0.10 mg/kg).

An MRL of 0.5 mg/kg is recommended for bicyclopyrone on AF 0081 Forage of cereal grains.

4.7 Rotational crops

Low residues were observed in the following crops spinach, radish and wheat, at plant back intervals of 87–90, 150–153 and 263–270 days in a bicyclopyrone field rotational study, after an application rate of 202–213 g ai/ ha (4.5–4.7× the maximum proposed application rate for bicyclopyrone on wheat and barley). It is therefore considered unlikely that any following crops could take up residues at a quantifiable level, noting that the Applicant has proposed re-cropping intervals of 4 months for summer crops and pastures and 9 months for winter crops and pastures.

4.8 Animal commodity MRLs

For beef and dairy cattle the estimated maximum livestock burden for bicyclopyrone is 0.183 ppm, based on a diet of 50% each for wheat and barley forage.

Beef and Dairy Cattle- 500 kg bw, 20 kg DM/day

FEED GROUP	COMMODITY	% IN DIET	FEED INTAKE (kg)	RESIDUE, MG/KG	% DM	LIVESTOCK DIETARY EXPOSURE		
						mg/animal	ppm	mg/kg bw
Barley	Forage	50	10	0.251	100	2.51	0.1255	0.00502
Wheat	Forage	50	10	0.115	100	1.15	0.0575	0.0023
Total		100	20			3.66	0.183	0.00732

An animal transfer study was considered in which lactating cattle were dosed with bicyclopyrone for 28 days. The predicted residues of bicyclopyrone in the milk and tissues of cattle fed with a 0.183 ppm dietary burden are shown in the following table.

Beef and dairy cattle

FEEDING LEVEL (ppm)	MILK	MUSCLE	LIVER	KIDNEY	FAT
	TOTAL BICYCLOPYRONE RESIDUE (mg/kg)				
3.0	<0.02	<0.02			<0.02
0.148			1.02	0.34	
0.183–beef and dairy cattle, estimated maximum burden	<0.02	<0.02	1.26	0.42	<0.02
Recommended MRLs	*0.02	*0.02	2 (edible offal based on liver)		Not necessary

Total bicyclopyrone residues are residues of SYN503780 + CSCD686480 expressed as bicyclopyrone equivalents

The likelihood of detectable residues occurring in milk, muscle and fat as a result of the proposed use is very low. It is appropriate to establish meat (mammalian) and milk MRLs at the LOQ of *0.02 mg/kg. An MRL for bicyclopyrone in edible offal of 2 mg/kg is appropriate based on the estimated high residue of 1.26 mg/kg in liver. Therefore the following MRLs are recommended:

MO 0105 Edible offal (mammalian) 2 mg/kg

MM 0095 Meat (mammalian) *0.02 mg/kg

ML 0106 Milks *0.02 mg/kg.

Barley and wheat grain and wheat milled by-products are significant poultry feeds. The maximum dietary burdens for poultry broilers and layers are 0.0155 and 0.0142 ppm respectively. The maximum estimated poultry dietary burden is much lower than the dose level in the submitted poultry metabolism study, in which poultry were dosed for 10 consecutive days at a nominal dose level of 20 mg bicyclopyrone/ kg of dry diet (approximately 1300–1400× times higher than the calculated maximum dietary exposure of poultry to bicyclopyrone). The predicted residues of bicyclopyrone in the eggs and tissues of poultry fed with a 0.0155 or 0.0142 ppm dietary burden are shown in the following table.

SAMPLE	RADIOACTIVE RESIDUES USING PYRIDINYL LABEL (AFTER FEEDING AT 20 ppm)	PREDICTED RESIDUES AFTER FEEDING AT 0.0155 ppm (LIVER, MUSCLE, FAT) OR AT 0.0142 ppm IN EGGS	RADIOACTIVE RESIDUES USING BICYCLOPYRONE LABEL (AFTER FEEDING AT 20 ppm)	PREDICTED RESIDUES AFTER FEEDING AT 0.0155 ppm (LIVER, MUSCLE, FAT) OR AT 0.0142 ppm IN EGGS
Egg yolk	0.104	0.00074	0.101	0.000072
Egg white	0.127	0.000090	0.086	0.000061
Liver	1.752	0.00136	1.776	0.00138
Composite muscle	0.136	0.000105	0.084	0.000105
Peritoneal fat	0.160	0.00012	0.178	0.00014
Skin and subcutaneous fat	0.536	0.000415	0.416	0.000322

The following MRLs are recommended:

PE 0112 Eggs *0.02 mg/kg

PO 0111 Poultry, Edible offal of *0.02 mg/kg

PM 0110 Poultry meat *0.02 mg/kg.

4.9 Estimated dietary intake

Chronic dietary exposure assessment

The chronic dietary exposure to bicyclopyrone is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for bicyclopyrone is equivalent to < 40% of the ADI.

It is concluded that the chronic dietary exposure is acceptable.

Acute dietary exposure assessment

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 with 97.5th percentile food consumption data derived primarily 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. A NESTI calculation was only made for the general population, and not for the 2–6 year old cohort, as the ARfD applies only to women of child bearing age.

The highest acute dietary intake was estimated at <70% of the ARfD (edible offal, 2+ cohort). The NESTIs for all other relevant commodities were < 10%. It is concluded that the acute dietary exposure is acceptable.

[2] WHO (2008). Consultations and workshops: Dietary Exposure Assessment of Chemicals in Food: Report of a joint FAO/WHO Consultation, Annapolis, Maryland, USA, 2-6 May 2005.

4.10 Bioaccumulation potential

Bicyclopyrone has an octanol/water partition coefficient (log10POW) of 0.25 at pH 5, -1.2 at pH 7 and -1.9 at pH 9. The Kow log P values are much lower than the cut-off designating a chemical as fat soluble (log P = 3)[3] indicating that bicyclopyrone is unlikely to partition preferentially into fat.

This conclusion is supported by the results of the feeding studies on lactating cows, where the rank order of residues of bicyclopyrone or residues of bicyclopyrone and structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 in edible tissues at the 10× treatment regime was: liver > kidney > fat and muscle (no quantifiable residues were observed in fat or muscle). In the lactating cow and laying hen metabolism studies, bicyclopyrone was observed in both muscle and fat in both the pyridinyl and bicyclooctenone label studies, but the highest tissue residues were observed in liver (hens and goats) and kidney (goats).

It is concluded that the potential for bioaccumulation of bicyclopyrone and structurally related metabolites is low.

4.11 Recommendations

The following amendments to the APVMA MRL Standard are required for the current application:

Table 5

COMPOUND	FOOD	MRL (mg/kg)
ADD:		
Bicyclopyrone		
GC 0640	Barley	0.02
MO 0105	Edible offal (Mammalian)	2
PE 0112	Eggs	*0.02
MM 0095	Meat (Mammalian)	*0.02
ML 0106	Milk	*0.02
PO 0111	Poultry edible offal, of	*0.02
PM 0110	Poultry meat	*0.02
GC 0654	Wheat	0.02
CM 0654	Wheat bran, unprocessed	0.05

[3] Pesticide Residues In Food—2005, Report pp. 27–31 (JMPR).

Table 3

COMPOUND	RESIDUE
ADD:	
Bicyclopyrone	Bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CDCD686480 and expressed as bicyclopyrone

Table 4

COMPOUND	ANIMAL FEED COMMODITY	MRL (mg/kg)
ADD:		
Bicyclopyrone		
AF 0081	Forage of cereal grains	0.5
AS 0081	Straw and fodder (dry) of cereal grains	0.2

MRL amendments recommended for Tables 1 and 3 above will be considered for inclusion in Schedule 20 of the Australia New Zealand Food Standards Code.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Wheat and barley are considered to be major export commodities[4], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated wheat and barley. Residues in these commodities resulting from the use of Talinor Herbicide may have the potential to unduly prejudice trade.

5.2 Destination of exports

Australian exports of wheat totalled 15,777 kt and were valued at $5,120 m in 2015–16. Australian exports of barley totalled 5,498 kt and were valued at $1,790 m in 2015–16[5].

Major export markets for Australian barley and wheat are presented below.

GRAIN	MAJOR DESTINATIONS
Barley	Asia including China, Japan, Rep. of Korea, Vietnam and Philippines; Middle East including Saudi Arabia, United Arab Emirates and Kuwait
Wheat	Asia including Indonesia, China, Vietnam, Rep. of Korea, Japan, Malaysia, Philippines and Thailand; Middle East including Yemen, Kuwait, United Arab Emirates, Oman, Iran and Iraq; Oceania including New Zealand, Papua New Guinea and Fiji; Africa including Nigeria, Egypt, Mozambique and South Africa

The significant export markets for Australian beef, sheep, pig meat and offals are listed in the APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B).

5.3 Proposed Australian use-pattern

The proposed use pattern is as a foliar spray applied in a tank mix with the registered Adigor Spray Adjuvant (60114) for the early post-emergent control and suppression of broadleaf weeds in wheat (except durum wheat) and barley (between wheat and barley crop stages GS12 and GS32). Refer to the draft label for details.

[4] APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B)

[5] Agricultural Commodity Statistics 2016, December 2016

5.4 Overseas registration and approved label instructions

The applicant indicated that the EC formulation containing 200 g/L bicyclopyrone is registered in the USA for uses in corn.

The ZC formulation (combination of capsule suspension (CS) and suspension concentrate (SC) containing 7.1 g/L bicyclopyrone, 12.8 g/L benoxacor, 120 g/L atrazine, 28.5 g/L mesotrione and 257 g/L S-metolachlor) is registered in the USA for use in corn and in Canada for use on corn and sweet corn.

5.5 Comparison of Australian MRLs with Codex and International MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Bicyclopyrone has not been considered by Codex. The following relevant overseas MRLs have been established for bicyclopyrone:

Relevant overseas MRLs/tolerances for bicyclopyrone

COMMODITY	MRLS FOR BICYCLOPYRONE (mg/kg)		
	AUSTRALIA	CANADA[6]	USA[7]
Residue Definition	Bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CDCD686480 and expressed as bicyclopyrone	4-hydroxy-3-{2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridinylcarbonyl}bicylo[3.2.1]oct-3-en-2-one) and its structurally related metabolites determined as the common moieties SYN503780 (expressed as bicyclopyrone equivalents) and CDCD686480 (expressed as CSAA915194 equivalents)	Sum of the common moieties SYN503780 (2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridinecarboxylic acid) and CSCD686480 (2-[(2-hydroxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridinecarboxylic acid), calculated as the stoichiometric equivalent of bicyclopyrone, in or on the commodities
Barley	0.02[1]		0.07
Wheat	0.02[1]		0.04
Wheat bran, unprocessed	0.05[1]		0.07
Edible offal (Mammalian)	2[1]	1.5 (cattle, sheep)	2 (cattle, hog, goat, sheep)

[6] http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/food-nourriture/mrl-lmr-eng.php

[7] http://www.ecfr.gov

COMMODITY	MRLS FOR BICYCLOPYRONE (mg/kg)		
	AUSTRALIA	CANADA[6]	USA[7]
Eggs	*0.02[1]	0.02	
Meat [mammalian]	*0.02[1]	0.02	
Milks	*0.02[1]		
Poultry, Edible offal of	*0.02[1]	0.02	
Poultry fat		0.02	
Poultry meat	*0.02[1]		

[1]Proposed

5.6 Potential risk to trade

Export of treated produce containing finite (measurable) residues of bicyclopyrone may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

The residue definition proposed for Australia is the same or similar to those established in markets overseas.

Key Australian barley and wheat export markets have not established bicyclopyrone MRLs for barley and wheat. Although finite MRLs at the LOQ of 0.02 mg/kg[8] have been established for bicyclopyrone in barley and wheat, quantifiable residues are not expected when the product is used as directed, so the potential risk to trade is considered to be low. MRLs are established in the USA for barley and wheat at 0.07 and 0.04 mg/kg respectively.

All animal commodities MRLs will be established at the LOQ (*0.02 mg/kg), except for edible offal (2 mg/kg). The calculated maximum residues of bicyclopyrone in edible offal are 1.26 mg/kg, based on an estimated maximum dietary burden of 0.183 ppm in beef and dairy cattle and based on residues of 1.02 mg/kg in liver in the lactating cattle feeding study after feeding at 0.148 ppm for 28 days.

It is noted that MRLs are established in Canada and the USA for meat by-products at 1.5 and 2 mg/kg respectively.

[8] Note: The individual LOQs for SYN503780 and CSCD686480 were 0.005 mg/kg (equivalent to 0.01 mg/kg bicylopyrone and CSAA915194). It is therefore considered that the combined LOQ should be 0.02 mg/kg as bicyclopyrone equivalents.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Formulation, packaging, transport, storage and retailing

The active constituent bicyclopyrone will be manufactured overseas. The product Talinor Herbicide will be formulated overseas and in Australia. Talinor Herbicide will be available in HDPE or PET containers, in sizes of 5 to 1000 L.

6.2 Use pattern

The proposed use pattern is as a foliar spray applied in a tank mix with the registered Adigor Spray Adjuvant (60114) for the early post-emergent control and suppression of broadleaf weeds in wheat (except durum wheat) and barley (between wheat and barley crop stages GS12 and GS32).

The product is to be applied by ground application equipment (ground boom only), at product rates between 500 and 1200 mL per hectare depending on the species and size of the target weeds, applied in water volumes of 100 L per hectare. The maximum area treated per day is up to 120 hectares.

6.3 Exposure during use

The product, Talinor Herbicide, will be used in commercial situations, by farmers, their employees and contract sprayers. Workers may be exposed to the product when opening containers, mixing/loading, during application of the product, and cleaning up spills and equipment. The main routes of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.

An exposure assessment was conducted, in conjunction with the hazard profile used to determine whether the proposed use of the product would be an undue health hazard to humans. In the absence of exposure data for the proposed mode of application, the US EPA Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate exposure to the three active constituents. For the purposes of modelling occupational exposure, the toxic endpoint of concern and identified NOAEL (1 mg/kg bw/d) for bicyclopyrone was derived from a developmental toxicity study in rabbits, and in this instance a margin of exposure (MOE) of 300 or above was considered acceptable. For bromoxynil octanoate, the appropriate NOAEL was 1 mg/kg bw/d from a 13 week oral dog toxicity study and a MOE of 100 or more was considered acceptable. For cloquintocet-mexyl, the appropriate NOAEL was 2 mg/kg bw/d from a 3–month dietary rat study and similarly a MOE of 100 or above was considered acceptable.

The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment for workers mixing/loading and applying the product to wheat or barley using ground boom equipment, the MOE are considered to be acceptable, providing closed mixing and loading equipment is used, and workers wear overalls over normal clothing and elbow-length chemical resistant gloves (i.e. personal protective equipment (PPE)).

As the general public are unlikely to be exposed to the product under normal conditions of use, the risk to the public was considered negligible.

6.4 Exposure during re-entry

Estimates of dermal exposure for the three active constituents from re-entering treated areas were undertaken using the US EPA Re-Entry Interval Calculator (2013). For post-application activities, the most appropriate NOAEL is normally taken from a short-term dermal toxicity study. The appropriate NOAEL for bromoxynil octanoate was 300 mg/kg bw/d from a 21–day rabbit dermal study with a MOE of 100 or more considered acceptable. Similarly for cloquintocet-mexyl, the appropriate NOAEL was 200 mg/kg bw/d from a 28–day rat dermal study with a MOE of 100 or above considered acceptable. However, the appropriate NOAEL for bicyclopyrone (1 mg/kg bw/d) was derived from a developmental toxicity study in rabbits, with a margin of exposure (MOE) of 300 or above considered acceptable.

The margins of exposure (MOEs) determined for re-entry activities associated with use of Talinor Herbicide were considered acceptable (MOE > 100) for bromoxynil octanoate and cloquintocet mexyl on day 0 for all crops and activities, and for bicyclopyrone (MOE > 300) for hand weeding activities in wheat, on day 0, and for scouting activities in wheat and barley, on day 16 after application.

6.5 Recommendations for safe use

Based on the human health risk assessment, Talinor Herbicide is supported for professional use, and users should follow the First Aid Instructions and Safety Directions, and observe the Precautions and Re-entry Interval stated on the product label.

6.6 Conclusion

The registration of Talinor Herbicide containing 175 g/L bromoxynil present as the octanoate, 37.5 g/L bicyclopyrone and 9.4 g/L cloquintocet-mexyl in an emulsifiable concentrate (EC) formulation, applied for the early post-emergent control and suppression of broadleaf weeds in wheat and barley, is supported.

Talinor Herbicide can be used safely if handled in accordance with the instructions on the product label.

7 ENVIRONMENTAL ASSESSMENT

Talinor Herbicide is an emulsifiable concentrate (EC) formulation containing 37.5 g/L bicyclopyrone and also 175 g/L of a previously approved active constituent bromoxynil (present as the octanoate) and the approved crop safener 9.4 g/L cloquintocet-mexyl. It is proposed to be used once annually using a MEDIUM spray quality, at rates of up to 1.2 L/ha as a post emergent herbicide for wheat and barley.

Environmental fate, behaviour and effects studies on bicyclopyrone and Talinor Herbicide have been provided as well as reference to existing uses of bromoxynil octanoate and cloquintocet-mexyl.

7.1 Environmental fate and behaviour

Hydrolysis

Bicyclopyrone is hydrolytically stable.

Photolysis/photodegredation

Photodegradation was shown to be a potentially major mechanism for degradation of bicyclopyrone with the main metabolite, SYN503780 found at up to 73% of the applied amount, which is significantly higher than that from the aerobic soil metabolism studies. Half-lives under laboratory conditions varied between 1.8 and 25.4 days in moist soil. In dry conditions the half-life is longer, with a DT50 of 59 days.

In field conditions, it was found that in soils where there are distinct rapid drying and wetting cycles that bicyclopyrone was being returned to the photolytic zone of the soil, allowing it to degrade more rapidly. However, in other climatic situations this is not expected to occur.

Bicyclopyrone also slowly degrades in aqueous environments with a half-life of 75 days in natural water. It does however, degrade more quickly in more acidic environments.

Fate and behaviour in soils

Under laboratory conditions in the dark, aerobic degradation of bicyclopyrone was highly variable, ranging from 19.8 days (readily degradable) to an extrapolated value of 434 days (very slightly degradable). Under field conditions, it is likely that photolysis significantly contributed to degradation with DT50 values ranging from 1.7 to 36 days.

All available data from radio-labelled and non-labelled studies indicates that the bicyclo-ring is degraded in soils, while the metabolites retain the aromatic pyridine ring. The metabolites produced under both aerobic and anaerobic conditions are SYN503780 (also known as SNAA794148 and CSAA806573), SYN454680 (also known as CSCD656832) and SYN504810 (also known as CSCC163768). Under laboratory conditions in the dark, SYN454680 was the only major metabolite reaching a maximum of 14.9% of the applied radioactivity (AR). In field conditions degradation showed a different major pathway. Consistent with the photolytic pathway SYN503780 is the major metabolite reaching up to 50% of the AR. The metabolite

SYN503780 rapidly degraded with half-lives of less than 5.2 days. Further studies showed that SYN454680 and SYN504810 are metabolites of SYN503780.

Fate and behaviour in water

Bicyclopyrone is very slightly degradable in aerobic and anaerobic water/sediment systems with extrapolated half-lives of up to 681 days in aerobic systems. As expected, no major transformation products were detected. The rate of dissipation from the water column in aerobic systems was not calculated but bicyclopyrone showed limited removal from the water column, with 69–74% remaining after 105 days.

By contrast when the tests were repeated under artificial sunlight under aerobic conditions the half-lives in the whole system were much faster with values between 7.4 and 7.5 days. The fraction of degradation products was also much larger. Much of it was unextractable, particularly for the bicyclooctenone label (both systems over 60% in 29 days). Two major metabolites were found, CSCC163768 (43.4–50.1% from the pyridine label only), and CSAA456156 around 20% forming from both labels. This is a major metabolite not found in any studies on photolysis or aerobic degradation of bicyclopyrone. It retains the parent structure but is simply demethylated. While there were some minor metabolites, CSAA589691, the primary degradate from the aqueous photolysis study was not found.

An outdoor multi-species test was conducted to determine the effects of bicyclopyrone to aquatic macrophytes exposed in outdoor microcosms and the kinetics of dissipation from the water phase was also modelled. Bicyclopyrone did not readily dissipate from the water column in the different microcosms with half-lives in the water averaging between two and three months.

Mobility

Bicyclopyrone was found to have very high mobility (KOC 0-50) in most soils (17 of the 23 tested). The lowest value for Koc is 6 mL/g. In three other soils, it was found to have a high mobility (KOC 50-150), and in the remaining three soils it was found to have a medium mobility (KOC 150-500). There was little correlation between organic carbon and adsorption (r = 0.11), suggesting mechanisms other than adsorption to organic carbon are prevalent. In all cases it was demonstrated that the adsorption is not fully reversible, however the degree to which this was shown varied.

In studies where bicyclopyrone was applied annually, there was a rise in frequency and concentrations of bicyclopyrone in groundwater in down-gradient wells, with no apparent plateauing of concentrations was detected. Modelling of the concentration of bicyclopyrone was also used and was found to under predict in comparison with the measured values, by a factor of approximately six.

Bioaccumulation

The logKOW is less than 0.25, and as such is not expected to bioaccumulate.

7.2 Environmental effects

Table 5: Toxicity of the active constituent bicyclopyrone to various organisms

ORGANISM		MEASURE OF TOXICITY OR EFFECT	PARAMETER (TEST PERIOD)	TOXICITY (UNIT)
Terrestrial species				
Bird	Bobwhite quail	Acute toxicity (oral)	LD50 1206	mg ac/kg bw
	Bobwhite quail,	Short term dietary exposure	LC50 (8 d) >1495	mg ac/kg body weight/day
	Mallard duck	Reproduction	(21 week) NOAEL 9.1	mg ac/kg bw/d
Honeybee (*Apis mellifera*)		Oral and contact toxicity	LD_{50} 48 h >200 oral/contact	µg/bee
Non-target arthropods	parasitoid (*Aphidius rhopalosiphi*)	Tier 2 dose/response	LR_{50} > 200	g ac/ha
	predatory mite (*Typhlodromus pyri*)	Tier 1 dose/response	LR_{50} > 200	
	Earthworm	Acute toxicity	LC_{50} 14 d >1000	mg/kg d.w.
Plants	Cabbage	Seedling emergence test	ER50 16.7	g ac/ha
	Turnip	Vegetative Vigour	LR50 24.9	
Aquatic species				
Fish	Rainbow trout	Acute toxicity	LD_{50} (96 h) > 93	mg ac/L
	Fathead minnow	Early life stage toxicity	NOEC (33 d) ≥ 10	mg ac/L
Aquatic invertebrate	*Daphnia magna*	Acute toxicity	EC_{50} > 93.3	mg ac/L
	Daphnia magna	Reproduction	NOEC (21 d) ≥ 103.7	mg ac/L
	Mysid shrimp (*Americamysis bahia*)	Acute, static	LC50 (96 h) = 3.4	mg ac/L
	Eastern oyster (*Crassostrea virginica*)	Acute, flow-through	EC50 (96 h) = 37	mg ac/L
Aquatic plants	*Lemna gibba*	Growth inhibition	EC_{50} = 0.055 (frond numbers); 0.073 (dry weight)	mg ac/L
	Brooklime (*Veronica beccabunga*)	Outdoor multispecies 82 days	EC_{10} = 1.1	µg ac/L

ORGANISM		MEASURE OF TOXICITY OR EFFECT	PARAMETER (TEST PERIOD)	TOXICITY (UNIT)
Algae	*Pseudokirchneriella subcapitata*	Growth inhibition	E_rC_{50} (96 h) = 5.9	mg ac/L
	Skeletonema costatum (marine species)		E_rC_{50} (96 h) = 9.2	
	Anabaena flos-aquae		E_rC_{50} (96 h) > 94.8	
	Navicula pelliculosa)		E_rC_{50} (96 h) = *20.7*	

Terrestrial organisms

Bicyclopyrone is considered to be slightly toxic to birds on an acute basis with an LD50 of 1206 mg ac/kg and the long-term NOAEL was determined to be 9.1 mg/kg bw/d. It is considered to be practically non-toxic to mammals on an acute basis, but has a long-term NOAEL of 1.9 mg/kg bw/d. There were no observed acute effects to bees, non-target arthropods, earthworms and soil micro-organisms at the highest rates tested.

Terrestrial Plants

A seedling emergence study was conducted with eleven species of terrestrial non-target plants (four monocots and seven dicots) exposed up to 8000 mL/ha of an emulsifiable concentrate (EC) formulation of bicyclopyrone containing with 150 g ac/L (1200 g ac/ha). The pre-emergent application of the bicyclopyrone formulation did not appear to result in a delay or inhibition of seedling emergence in any of the species tested. However, phytoxicity was demonstrated to all test species and the most sensitive species was cabbage with an ER50 based on biomass of 16.7 g ac /ha.

In a vegetative vigour study (post-emergence application), eleven species of terrestrial non-target plants (four monocots and seven dicots) were exposed to nominal application rates of 8000 mL/ha formulation containing 150 g ac/ha, equivalent to 1200 g ac/ha. All plants tested showed sensitivity with a reduction in biomass. Treatment resulted in a reduction in non-target plant survival after 21 days in the monocot onion and dicot turnip. In general, dicots appear to be more sensitive than the monocots tested. The most sensitive bounded 21 day survival LR50s endpoint in the vegetative vigour study was 24.9 g ac/ha. The most sensitive 21 day survival LR25 was > 2.78 g ac/ha, again for these two plant species. The most sensitive 21 day height ER50, ER25 and NOER values were identified in the sunflower, being, respectively, 2.60, 1.23 and 0.31 g ac/ha. The sunflower also has the most sensitive biomass 21 day endpoints for the ER50, ER25 and NOER with respective values of 1.50, 0.92 and 0.31 g ac/ha. There are several options for determining the regulatory acceptable level (RAL) but currently the LR50 ÷ 10, of the most sensitive species is preferred when there are multiple options. This results in an RAL of 2.49 g ac/ha.

Aquatic organisms

Bicyclopyrone is expected to, at worst, be slightly toxic to fish on an acute and chronic basis. Similarly, freshwater invertebrates showed no sensitivity to bicyclopyrone on an acute or chronic basis. Estuarine species (shrimp and oysters) showed greater sensitivity and bicyclopyrone is considered slightly to moderately toxic to these species. Sediment dwelling organisms are not expected to be sensitive to bicyclopyrone based on the low toxicity to freshwater invertebrates and bicyclopyrone's propensity to remain in the aquatic compartment.

Bicyclopyrone was moderately toxic to practically non-toxic to the four standard algal species with 96 h ErC50 values ranging from 5.9 to >94.8 mg ac/L. However, bicyclopyrone is very highly toxic to the standard floating aquatic macrophyte, Lemna gibba, with the most sensitive 7 d ErC50s of 55 and 73 µg ac/L for inhibition of yield based on frond numbers and plant dry weights, respectively. A higher tier outdoor multi-species study on bicyclopyrone, simulating more realistic aquatic ecosystems was conducted for 82 days. Several species in the control of the study were found not to have grown and it is likely that this was due to overcrowding of species competing for nutrients. These were not included in the analysis. Of the remaining species, Brooklime (*Veronica beccabunga*) was the most sensitive with an ErC10 of 1.1 µg ac/L. Based on this value with no additional safety factor a regulatory acceptable concentration (RAC) of 1.1 µg ac/L has been established.

7.3 Risk assessment

A standard environmental risk assessment was conducted on Talinor Herbicide. At least two of the active constituents of Talinor Herbicide were not acutely toxic to mammals, bees, earthworms and soil micro-organisms and the remaining active constituent was either not acutely toxic or presented lower risk to these organisms than the nominated reference products.

Acute toxicity to birds from Talinor Herbicide was identified as being due to the bromoxynil content rather than bicyclopyrone content, but the potential risk to birds from use of Talinor herbicide is not expected to be any greater than for currently registered uses of bromoxynil. The chronic risk to native animals consuming foliage sprayed with bicylopyrone at the proposed rates is considered acceptable.

The risk to aquatic organisms in aquatic systems entirely fed by groundwater discharge containing bicylcopyrone leached from treated fields, was modelled then calibrated by multiplying by a factor of six to reflect measured values from studies. This value was below the RAC for bicylcopyrone and therefore the risk is considered acceptable. Similarly the risk to the aquatic environment from run-off, of bicylcopyone from adjacent fields treated with Talinor Herbicide is considered acceptable, when modelled at a screening level.

Standard spray drift risk assessments were undertaken for protection of aquatic life and terrestrial plants for Talinor Herbicide. The eco-toxicity of the product was determined using the concentration addition method supplemented by the applicant's studies. The most sensitive aquatic species are aquatic invertebrates with an EC50 of 43 µg product/L, and this toxicity was driven by bromoxynil octanoate. The spray drift risk assessment was conducted using the spray quality (MEDIUM) proposed on the label for Talinor Herbicide.

A regulatory acceptable concentration (RAC) of 0.0043 mg/L (4.3 µg product/L) in the aquatic environment, was calculated from the EC50 of the product. To achieve concentrations in the aquatic environment below the RAC, a downwind no-spray zone of 25 m is required.

For terrestrial plants, the eco-toxicity of the product was determined using the applicant's studies, which was broadly consistent with the concentration addition method, for the active constituents. Based on the most sensitive plant species, which has a vegetative vigour ER50 of 90.2 g product/ha a regulatory acceptable level (RAL) of 9.02 g product/ha, was determined.

To achieve a level of exposure to non-target plants below the RAL, a downwind no-spray zone of 20 m is required.

7.4 Conclusion

The risk assessment has considered the risks of bicyclopyrone alone and the combination product Talinor Herbicide. In considering the submitted data particular attention has been given to the potential risk to organisms in aquatic and terrestrial environments and downwind no-spray zones are recommended to mitigate these risks.

The APVMA is satisfied that risks resulting from use of Talinor Herbicide will be acceptable providing all label instructions are followed.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

Talinor Herbicide is a selective herbicide. The proposed use pattern is as a foliar spray applied in a tank mix with the registered Adigor Spray Adjuvant (60114) for the early post-emergent control and suppression of broadleaf weeds in wheat (except durum wheat) and barley (between wheat and barley crop stages GS12 and GS32). The addition of cloquintocet-mexyl as an herbicide safener, is to reduce the effect of the herbicide on crop plants.

The product is to be applied by ground application equipment, at product rates between 500 and 1200 mL per hectare depending on the species and size of the target weeds. A range of rates may be used for certain uses and higher product rates are indicated where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rates should also be used when environmental conditions are marginal, such as low soil moisture.

8.2 Assessment of study/trial data

Efficacy

Talinor Herbicide was evaluated for efficacy on 40 broadleaf weeds in 82 field trials in Queensland, NSW, Victoria, Tasmania, South Australia and Western Australia over several seasons.

Weed species included:

Capeweed, *Arctotheca calendula,* Bifora, *Bifora testiculata,* Volunteer Canola, *Brassica napus,* White Iron weed, Buglossoides arvensis, Shepherd's purse, Capsella bursa-pastoris, Saffron Thistle, *Carthamus lanatus,* Chickpea, *Cicer arietinum,* Flax-leaf fleabane, *Conyza bonariensis,* Paterson's Curse, *Echium plantagineum,* Spiny emex, *Emex australis,* Broadleaf Erodium, *Erodium botrys,* Common Storksbill, *Erodium cicutarium,* Black Bindweed, *Fallopia convolvulus,* Bastard's Fumitory, *Fumaria bastardii,* Dense-flower Fumitory, *Fumaria densiflora,* Wall Fumitory, *Fumaria muralis,* Common Fumitory, *Fumaria officinalis,* Small-flowered Fumitory, *Fumaria parviflora,* Three-horned Bedstraw, *Galium tricornatum,* Prickly Lettuce, *Lactuca serriola,* Deadnettle, *Lamium amplexicaule,* Lentils, *Lens culinaris,* Lupins, *Lupinus angustifolius,* Burr Medic, *Medicago polymorpha,* Snail Medic, *Medicago scutellate,* Medic, *Medicago spp.,* Ball Mustard, *Neslia paniculata,* Field Peas, *Pisum sativum,* Wireweed, *Polygonum aviculare,* Wild Radish, *Raphanus raphanistrum,* Turnip Weed, *Rapistrum rugosum,* Charlock, *Sinapis arvensis,* Hedge Mustard, S*isymbrium officinale,* Indian Hedge Mustard, *Sisymbrium orientale,* Sowthistle, *Sonchus oleraceus,* Chickweed, *Stellaria media,* Sub Clover, *Trifolium subterraneum,* Faba Beans, *Vicia faba,* Spurred Vetch, *Vicia monantha* and Vetch, *Vicia sativa.* Trials targeted broadleaf weeds for early post-emergent use (between GS12 and GS32) in wheat and barley.

The trials used scientific methodology and appropriate assessment parameters and incorporated 3 or 4 replicates, one or multiple industry standards and untreated controls. Results were analysed using standard statistical procedures (ANOVA, Multiple regression analysis, LSD).

Multiple industry standards were used in efficacy and crop safety trials at label rates and in some cases higher rates. Talinor herbicide was applied at 250 to 1250 mL/ha in efficacy trials and from 667 to 2667 mL/ha in crop safety and plantback trials and compared at equivalent rates to industry standards.

Efficacy trials were assessed at intervals up to 68 days after treatment by measurement or assessment of percentage weed control, reduction in weed biomass relative to the untreated control and percentage biomass or biomass reduction.

Most weed species were controlled at rates between 500 and 750 mL/ha, though some required up to 1200 mL/ha particularly for larger plants and higher weed densities.

Trial data are supportive of efficacy of Talinor Herbicide for control of the broadleaf weed species as listed on the proposed label.

Crop safety

Crop safety, evaluated in both dedicated crop safety trials as well as in efficacy trial work, was confirmed in southern latitudes of the cereal growing regions of Australia. Some transient phytotoxicity was encountered in northern cereal growing regions as a result of environmental influences prior to and soon after application. Analysis of environmental conditions at the time of application has clearly identified factors that increase the risk of crop damage. These factors have been incorporated into label restraints and instructions and can be managed by growers in commercial situations.

Plantback evaluations conducted across multiple growing seasons highlighted strong safety to following crops, both summer and winter. Plantback intervals were determined for 14 winter crop and pasture species and 10 summer crop species and these are identified on the product label.

Tank mixes

Talinor Herbicide is recommended for use as a tank mix with Adigor Spray Adjuvant (60114), at an adjuvant product rate of 500 mL per 100 L water, and satisfactory evidence of efficacy and crop safety of the mixture was provided to justify its inclusion in the label instructions.

Resistance management

Bicyclopyrone is a member of the triketone sub-group of the class of herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (4-HPPD). There are no herbicides of the triketone sub-group currently registered in Australia. The 4-HPPD inhibiting herbicides are referred to as Group H herbicides in Australia and achieve herbicidal activity by preventing the catabolism of tyrosine. This has two key outcomes, oxidative damage in leaf tissue due to a lack of tocopherols and the break-down of chlorophyll due to a reduction in carotenoids. These outcomes produce the typical 4-HPPD symptoms of bleaching, particularly in new leaf tissue.

Bromoxynil is a member of the Group C herbicides, in the nitrile sub-group. The Group C herbicides variously inhibit photosystem II by binding to the D1 protein found within the thylakoid membrane to block the binding of plastoquinone to the D1 protein. The result of this is that critical electron transfer between

Photosystem II and Photosystem I cannot occur and photosynthesis is halted. Additionally, the accumulation of electrons in the chloroplast results in the degradation of chlorophyll and carotenoids. Carotenoid degradation results in destruction of cellular tissues.

For weed resistance management purposes Talinor Herbicide is a Group C, H herbicide.

8.3 Conclusions

The product Talinor Herbicide, acts as a selective herbicide and can be used in specific wheat and barley crop situations without causing unacceptable damage to the crop, while providing acceptable control and suppression of a range of broadleaf weeds.

9 LABELLING REQUIREMENTS

POISON

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

syngenta®

ACTIVE CONSTITUENTS: 175 g/L BROMOXYNIL present as the octanoate
37.5 g/L BICYCLOPYRONE
9.4 g/L CLOQUINTOCET-MEXYL

SOLVENT: 338 g/L HYDROCARBONS, LIQUID

GROUP C H HERBICIDE

For the post-emergent control of a range of broadleaf weeds in Wheat and Barley

5–1000 LITRES

Syngenta Australia Pty Ltd
Level 1, 2-4 Lyonpark Road, Macquarie Park NSW 2113

In a transport emergency dial 000, Police or Fire Brigade
For specialist advice in an emergency only, call 1800 033 111 (24 hours)

APVMA Approval No.: 82256/105296

DIRECTIONS FOR USE

Restraints

DO NOT apply by air
DO NOT apply if rainfall is expected within 2 hours of application
DO NOT apply to weeds under stress from factors including very dry, waterlogged, cold or frosty conditions or nutrient deficiency
DO NOT apply with liquid urea ammonium nitrate (UAN) fertilisers
DO NOT apply with ammonium sulphate fertilisers
DO NOT apply more than 1 application per season
DO NOT apply after Cereal Growth Stage GS32

Spray Drift Restraints

DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the British Crop Production Council guideline.

DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour, as measured at the application site.

DO NOT apply during surface temperature inversion conditions at the application site.

Users of this product **MUST make an accurate written record** of the details of each spray application within 24 hours following application, and must KEEP this record for at least 2 years. The spray application details that must be recorded are:

1 date with start and finish times of application

2 location address and paddock(s) sprayed

3 full name of this product

4 amount of product used per hectare and number of hectares applied to

5 crop or situation and weed or pest

6 wind speed and direction during application

7 air temperature and relative humidity during application

8 nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application

9 name and address of person applying this product.

(Additional record details may be required by the state or territory where this product is used.)

Mandatory No-Spray Zones

DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within 25 metres downwind from the application area.

DO NOT apply if there are sensitive crops, gardens, landscaping vegetation, protected native vegetation or protected animal habitat within 20 metres downwind from the application area.

Crop	Weeds	Target Size	Product Rate (mL/ha)	Critical Comments
Wheat, Barley (GS12 to 32)	Wild Radish (*Raphanus raphanistrum*)	Up to 4 leaf	500 to 750 plus ADIGOR® at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal.
		Up to 6 leaf	750 to 1200 plus ADIGOR at 500 mL per 100 L water	
Crop	**Weeds**	**Target Size**	**Product Rate (mL/ha)**	**Critical Comments**
Wheat, Barley (GS12 to 32)	Ball Mustard (*Neslia paniculata*), Charlock (*Sinapis arvensis*), Hedge Mustard (*Sisymbrium officinale*), Indian Hedge Mustard (*Sisymbrium orientale*), Turnip Weed (*Rapistrum rugosum*) Volunteer Canola (*Brassica napus)*,	Up to 4 leaf	500 to 750 plus ADIGOR at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal.
		Up to 8 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	
	Prickly Lettuce (*Lactuca serriola*)	Up to 5 leaf	500 to 750 plus ADIGOR at 500 mL per 100 L water	
	Bastard's Fumitory (*Fumaria bastardii*), Common Fumitory (*Fumaria officinalis*), Dense-flower Fumitory (*Fumaria densiflora*), Small-flowered Fumitory (*Fumaria parviflora*), Wall Fumitory (*Fumaria muralis*), Patterson's Curse (*Echium plantagineum*), Sub Clover (*Trifoliu*m *subterraneum*), White Iron Weed (*Buglossoides arvensis*)	Up to 6 leaf	500 to 750 plus ADIGOR at 500 mL per 100 L water	

Crop	Weeds	Target Size	Product Rate (mL/ha)	Critical Comments
	Bifora (*Bifora testiculata*), Burr Medic (*Medicago polymorpha*), seedling Lucerne (*Medicago sativa*), Snail Medic (*Medicago scutellate*), Chickpeas (*Cier arietinum*), Faba Beans (*Vicia faba*), Field Peas (*Pisum sativum*), Lupins (*Lupinus angustifolius*), Spurred Vetch (*Vicia monantha*), Vetch (*Vicia sativa*), Deadnettle (*Lamium amplexicaule*) Sowthistle (*Sonchus oleraceus*)	Up to 8 leaf	500 to 750 plus ADIGOR at 500 mL per 100 L water	

Crop	Weeds	Target Size	Product Rate (mL/ha)	Critical Comments
Wheat, Barley (GS12 to 32)	Lentils (*Lens culinaris*)	Up to 5 leaf	500 plus ADIGOR at 500 mL per 100 L water (***suppression***)	Under higher target densities or at larger growth stages, the lower rate will substantially reduce the biomass of lentils but may not achieve commercially acceptable levels of control.
			750 plus ADIGOR at 500 mL per 100 L water	
	Capeweed (*Arctotheca calendula*)	Up to 6 leaf	500 to 750 plus ADIGOR at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal.
		Up to 8 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	
	Saffron Thistle (*Carthamus lanatus*)	Up to 6 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	

Crop	Weeds	Target Size	Product Rate (mL/ha)	Critical Comments
	Broadleaf Erodium (*Erodium botrys*) Common Storksbill (*Erodium cicutarium*)	Up to 4 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal. Shading as a result of high densities of Erodium may mean that regrowth occurs from plants that were only partially treated.
	Bindweed (*Fallopia convolvulus*) Wireweed (*Polygonum aviculare*)	Up to 3 leaf	500 plus ADIGOR at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal. Under low soil moisture conditions, control of Bindweed can be severely reduced.
		Up to 6 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	

Crop	Weeds	Target Size	Product Rate (mL/ha)	Critical Comments
Wheat, Barley (GS12 to 32)	Shepherd's Purse (*Capsella bursa-pastoris*)	Up to 4 leaf	500 plus ADIGOR at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal.
		Up to 8 leaf	750 plus ADIGOR at 500 mL per 100 L water	
	Spiny Emex/Double Gee (*Emex australis*)	Up to 2 leaf	500 plus ADIGOR at 500 mL per 100 L water	
		Up to 4 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	

Crop	Weeds	Target Size	Product Rate (mL/ha)	Critical Comments
	Chickweed (*Stellaria media*)	Up to 4 leaf	750 plus ADIGOR at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal. Control may be reduced where coverage of target weeds is compromised. Partially affected Chickweed may recover if coverage is inadequate.
	Suppression of Fleabane (*Conyza bonariensis*)	Up to 4 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	Plant numbers will be reduced but some recovery may occur in larger plants under marginal soil moisture conditions. Efficacy will be maximised when Autumn germinating Fleabane are targeted and excellent coverage of the weed is achieved.
	Suppression of Bedstraw (*Gallium tricornatum*)	Up to 4 leaf	750 to 1000 plus ADIGOR at 500 mL per 100 L water	Use the higher rate where the density of the target weed is high and/or the weeds are at more advanced growth stages. The higher rate should also be used when environmental conditions are marginal.

WITHHOLDING PERIODS

Harvest: NOT REQUIRED WHEN USED AS DIRECTED
Grazing: DO NOT GRAZE OR CUT FOR STOCK FEED FOR 6 WEEKS AFTER APPLICATION

EXPORT TRADE ADVICE – TREATED CEREALS: Grain harvested from cereal crops treated with TALINOR may contain finite (measurable) residues of bicyclopyrone and may pose a risk to trade in situations where no residue tolerance (import tolerance) is established in the importing country or where residues in Australian commodities are likely to exceed a residue tolerance (import tolerance) established in the importing country. Before you use this product, you are advised to contact Syngenta and/or your industry body about any potential trade issues and their management. If you use this product and grain harvested from treated crops is destined for export, you are required to declare the use of TALINOR to buyers of the grain, when requested or when required by contract or trade terms.

GENERAL INSTRUCTIONS

TALINOR Herbicide is a foliar applied post-emergent herbicide containing the active ingredients bicyclopyrone, a Group H triketone herbicide, and bromoxynil, a Group C nitrile herbicide. TALINOR is predominantly taken up through leaf tissue, with very little absorption through plant roots and does not provide residual control of weeds that germinate after application. Bicyclopyrone causes the rapid breakdown of chlorophyll in leaf tissue, resulting in bleaching of leaf tissue. Bromoxynil blocks the activity of Photosystem II, leading to cessation of photosynthesis and destruction of leaf tissues.
TALINOR should only be applied to weeds that are actively growing and not suffering stress, especially in the case of low soil moisture. In the event of application to stressed weeds, reduced efficacy may result and treated plants may recover. However, their biomass will be substantially reduced and their competitiveness will be lower.

Because of the contact nature of bicyclopyrone and bromoxynil, the efficacy of TALINOR is heavily dependent on good coverage of target weeds. The rapid speed of activity of TALINOR means that translocation is limited, with lower activity in areas of the plant not directly treated at application. As a result, when weeds are shaded due to large size, high densities or because of coverage from an advanced crop canopy, efficacy is likely to be reduced and treated plants may recover. However, their biomass will be substantially reduced and their competitiveness will be lower.

TALINOR efficacy will be maximised when applied early in the season (2 to 5 leaf crop growth stage) while shading of weeds by the crop canopy or from other weeds is minimised. A follow up application of another herbicide may be required if subsequent germinations occur.

In Queensland, Northern New South Wales and the Northern Ag Region of Western Australia, higher light intensity and warmer temperatures mean there is a greater risk of crop phytotoxicity, particularly in wheat. In these areas, applying TALINOR in the afternoon or at night, particularly where overnight minimum temperatures in the week prior to application are mild and frost-free, to crops that are growing rapidly will exacerbate this risk. Refer to the Crop Safety section for further detail.

Full details of application and environmental factors that can affect TALINOR efficacy and crop safety are listed below and should be reviewed before use.

Mixing

TALINOR is an emulsifiable concentrate that mixes readily with water. Fill the spray tank to one quarter full. Add TALINOR and continue adding water to make up to the final spray volume. Agitate while mixing and spraying.

When tank mixing, wettable powder or water dispersible granule formulations should be added to the tank first followed by suspension concentrates (flowables), water soluble salts then TALINOR or other emulsifiable concentrate formulations. Maintain thorough agitation during mixing and application. Agitate tank mixes vigorously if allowed to stand. Note: Tank mix spray solutions should NOT be left standing in the vat overnight.

Compatibility

TALINOR is compatible with Agritone* 750, Lontrel* 750 SG and Lontrel* (300 g/L). ***Always refer to registered plant back restrictions on the label of the tank mix partner.*** Refer to your local Syngenta representative for the most up to date information relating to the compatibility and crop safety of herbicide tank mixtures.

TALINOR must NOT be mixed with liquid urea ammonium nitrate (UAN) or ammonium sulphate fertilisers (either granular or liquid) under any circumstances.

As formulations of other manufacturers' products are beyond the control of Syngenta and water quality varies with location, all mixtures should be tested prior to mixing commercial quantities.

Surfactant/Adjuvant

It is recommended that TALINOR be applied with ADIGOR Spray Adjuvant at 500 mL/100L of spray water. Hasten Spray Adjuvant may also be used at a rate of 1000 mL/100L of spray water. Non-ionic surfactants and soyal-lipid based adjuvants must NOT be used with TALINOR as a significant reduction in efficacy will occur.

Application

DO NOT apply by air.
DO NOT apply using a misting applicator.
TALINOR is sensitive to good coverage of the target weeds, so the highest water rate appropriate to the weed control scenario presented should be used. This is particularly important where coverage is already compromised due to shading of the target weeds, either through inter-weed shading or because of an advanced crop canopy.
Use a nozzle delivering spray quality in the medium spray range, with a minimum of 75L/ha of water volume up to 150L/ha.
Additionally, when targeting more advanced weeds, it is recommended that higher water rates are used, even where inter-weed or crop shading is minimal.

Crop Safety

DO NOT apply to durum wheat.
DO NOT apply to crops undersown with legumes.

Under some environmental conditions, crop phytotoxicity may be observed following the use of TALINOR. This is more likely to result in wheat than barley and presents as bleaching or yellowing of leaves, generally interveinal, that emerge in the period after spraying. The effect is transient and crop recovery, under good growing conditions, is rapid.

Use in northern growing regions (QLD, NNSW and the Northern Ag Region of Western Australia), where light intensity is greater is likely to increase the risk of crop phytotoxicity. However, under the following circumstances, the risk of phytotoxicity is greatly reduced;

1. Application early in the day - application in the morning reduces the severity and likelihood of crop damage.
2. When an application is made to a crop that has adequate soil moisture such that it is not stressed and is healthy. In particular, where a crop may have been suffering from moderate moisture stress, it is important to wait until useful rainfall has been received and the crop has recovered before making an application of TALINOR.
3. Cool minimum temperatures prior to application - moderate overnight temperatures will slow the rate of crop growth and allow recovery from stress conditions. Note however that low temperature, frosty conditions may compromise weed control and should be avoided.
4. Moderate maximum temperatures following application - avoid applying TALINOR if it is expected that temperatures will be warm in the 7 days following application, particularly if the crop is already well watered and growing rapidly.

Over application, due to boom overlap on headlands and at boom tips on adjacent passes of spraying equipment, is likely to increase both the likelihood and severity of crop damage. Care should be paid to ensure over application is minimized, particularly in northern growing regions.

Crop Rotation Recommendations

Minimum recropping intervals should be observed following the use of TALINOR. TALINOR is more rapidly degraded at higher soil pH, so carryover is more likely on acid soils.

Minimum rainfall or irrigation requirements apply for the stated recropping intervals to apply. Lower rainfall amounts may necessitate an extended recropping period. If patchy, light rainfall events occur with extended periods of dry weather between, sufficient soil moisture for effective breakdown of TALINOR may not be achieved, even if the minimum rainfall amount is achieved.

Plantback to Winter Crops and Pastures

Crop	TALINOR rate (mL/ha)	Minimum rainfall or irrigation required	Recropping interval
Wheat, barley, oats, triticale, canola, lupins, vetch, faba beans, lentils, field peas, sub-clover*, medic* and lucerne*	Up to 1200	250 mm	9 months

* Where TALINOR is applied at a rate of 1200 mL/ha on acid soils, seedling vigour reduction and reduced plant stand may occur. However, impacts on seedling vigour are expected to be transient and no long term impact is likely.

Areas that receive double rates, such as boom overlaps, may exhibit increased crop effect. Generally, this is a bleaching or yellowing of the crop and is expected to be transient but may be accompanied by a crop biomass reduction.

Plantback to Summer Crops and Pastures

Crop	TALINOR rate (mL/ha)	Minimum rainfall or irrigation required	Recropping interval
Maize, pigeon pea, cowpea, mungbean, adzuki bean, sorghum, cotton *, soybean *, sunflower *, safflower **	1200	150 mm	4 months

* Where TALINOR is applied at a rate of 1200 mL/ha, crop tolerance may be reduced if waterlogging occurs in the first 6 weeks after planting. However, phytotoxicity (in the form of bleaching or chlorosis) and crop biomass reductions are likely to be transient with full recovery expected and no impact on crop yield.

** Where TALINOR is applied at a rate of 1200 mL/ha, crop tolerance may be reduced if waterlogging occurs in the first 6 weeks after planting. Phytotoxicity (in the form of bleaching or chlorosis) and crop biomass reductions are possible along with minor reductions in crop yield.

Areas that receive double rates, such as boom overlaps, may exhibit increased crop effect. Generally, this is a bleaching or yellowing of the crop and is expected to be transient but may be accompanied by a crop biomass reduction.

Resistant Weeds Warning

TALINOR Herbicide contains members of the triketone (bicyclopyrone) and nitrile (bromoxynil) groups of herbicides. TALINOR works by inhibiting 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) and photosynthesis at photosystem II in treated plants. For weed resistance management, this product is a Group H and Group C herbicide. Some naturally occurring weed biotypes resistant to this product and other Group H or Group C herbicides may exist through normal genetic variability in any weed population. The resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly.

These resistant weeds will not be controlled by this product or other Group H or Group C herbicides. Since the occurrence of resistant weeds is difficult to detect prior to use, Syngenta Australia Pty Ltd accepts no liability for any losses that may result from the failure of this product to control resistant weeds. Advice as to strategies and alternative treatments that can be used should be obtained from your local supplier, consultant, local Department of Agriculture, Primary Industries Department or a Syngenta representative.

Resistance Management

Management of weed resistance to the Group H herbicides is important to maintain this critical Mode of Action (MoA) group, particularly for the management of multiple MoA resistant populations of Wild Radish. When using TALINOR, where practical, and particularly when targeting weed populations with developing resistance, the addition of another herbicide with a different MoA to TALINOR (Group H and C) should be considered. **Refer to your local Syngenta representative for the most up to date information relating to management of Group H herbicide resistance, or refer to the CropLife Australia Group H guidelines (www.croplife.com.au).**

DO NOT make more than one Group H based herbicide application per crop.

Management of weeds, particularly those suspected of already having developed herbicide resistance, with TALINOR should be a part of an Integrated Weed Management strategy designed around maximising control of weeds at all stages of their life cycle. The use of a diversity of herbicide Modes of Action, including TALINOR, should be considered to be one part of such a strategy. Additional, non-herbicidal, control practices should also be employed taking into account agronomic, mechanical and cultural techniques. **Refer to your local Syngenta representative for the most up to date information relating to Resistance Management or alternatively to the information available through the WeedSmart program.**

Integrated Pest Management

TALINOR Herbicide is not compatible with Integrated Pest Management.

PRECAUTION

DO NOT apply by air.

DO NOT apply using a misting applicator.

DO NOT use open mixing and loading equipment.

Re-entry Period: DO NOT enter treated areas for 16 days to perform scouting activities 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 CROPS, NATIVE AND OTHER NON-TARGET PLANTS

DO NOT apply under weather conditions or from spraying equipment which may cause spray to drift onto nearby susceptible plants/crops, cropping lands or pastures.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT.

Highly toxic to aquatic life. DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well ventilated area. DO NOT store for prolonged periods in direct sunlight.

Returnable containers

Empty contents fully into application equipment. Close all valves and return to point of supply for refill or storage.

Non-returnable containers

Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. 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.

SAFETY DIRECTIONS

Harmful if swallowed. May irritate eyes and skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. When opening the container, preparing spray and using the prepared spray, wear

- **cotton overalls, over normal clothing, buttoned to the neck and wrist**
- **elbow-length chemical resistant gloves.**

Wash hands after use. After each day's use, wash gloves and contaminated clothing.

FIRST AID

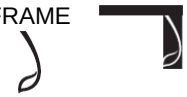
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone 131 126. If swallowed, DO NOT induce vomiting. Give a glass of water.

SAFETY DATA SHEET

If additional hazard information is required, refer to the Safety Data Sheet. For a copy phone 1800 067 108 or visit our website at www.syngenta.com.au

DISCLAIMER

This product complies with the specifications in its statutory registration. Implied terms and warranties are excluded. Syngenta's liability for breach of the express or any non-excludable implied warranty is limited to product replacement or purchase price refund. The purchaser must determine suitability for intended purpose and take all proper precautions in the handling, storage and use of the product including those on the label and/or safety data sheet failing which Syngenta shall have no liability.



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APVMA Approval No.: 82256/105296

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
C_{max}	maximum plasma concentrations
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
EC	Emulsifiable Concentrate
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{10}/EC_{50}	concentration at which 10%/50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ER_{25}/ER_{50}	Effective rate of a substance that causes 10%/50% of the maximum response
ESI	Export Slaughter Interval
EUP	End Use Product
FAO	Food and Agriculture Organisation
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice

GCP	Good Clinical Practice
GJR	Global Joint Review
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HPPD	4-hydroxyphenyl pyruvate dioxygenase
HR-P	Highest Predicted Residue Value
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
IV/iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint Meeting on Pesticide Residues (CODEX)
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
K_{ow}	Concentration in octanol phase/Concentration in aqueous phase
L	Litre
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
LOD	Limit of Detection—level at which residues can be detected
LOEL/LOAEL	Lowest Observed Effect Level/Lowest Observed Adverse Effect Level

LR_{25}/LR_{50}	Lethal rate of a substance that causes 25%/50% of the maximum response
LOQ	Limit of Quantitation—level at which residues can be quantified
mg	milligram
mL	millilitre
MoA	Mode of Action
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
MTD	maximum tolerated dose
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOAEC/NOAEL	No Observable Adverse Effect Concentration/Level
NOEC/NOEL	No Observable Effect Concentration/Level
NOER	No Observable Effect Rate
NTBC	nitisinone
NZW	New Zealand White (rabbits)
OC	Organic Carbon
OCS	Office of Chemical Safety
OM	Organic Matter
PMRA	Health Canada Pest Management Regulatory Agency
po	oral
P_{ow}	Octanol water partition coefficient
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million

Q-value	Quotient-value
RAC/RAL	Regulatory Acceptable Concentration/Level
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
STMR	Supervised Trial Median Residue
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total Radioactive Residue
TSH	thyroid stimulating hormone
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
UDPGT	uridine diphosphate glucuronyltransferase
µg	microgram
USEPA	United States Environmental Protection Agency
vmd	volume median diameter
WG	Water Dispersible Granule
WHO	World Health Organisation
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Percutaneous	Through the skin
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

Australian Pesticides and Veterinary Medicines Authority 2008, *Ag MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.

Australian Pesticides and Veterinary Medicines Authority 2008, *Vet MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.