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Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active topramezone in the product Frequency Herbicide

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator responsible for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia. Before approving an active constituent and/or registering a product, the APVMA must be satisfied that the statutory criteria, including the safety, efficacy, trade and labelling criteria, have been met. The information and technical data required by the APVMA to assess the statutory criteria of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the APVMA website.

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents. 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 advisory agencies, including other Australian Government agencies and State departments of primary industries. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

About this document

This is a Public Release Summary.

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

Submissions must be received by the APVMA by close of business on **14 May 2019** 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. Unless requested by the submitter, the APVMA may release a submission, with any CCI redacted, to the applicant for comment.

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 technical evaluation reports covering chemistry, efficacy and safety, 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.

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

1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Frequency Herbicide, containing the new active topramezone, in combination with the active cloquintocet-mexyl.

1.1 Applicant

BASF Australia Ltd.

1.2 Purpose of application

BASF Australia Ltd has applied to the APVMA for registration of the new product Frequency Herbicide, containing 60 g/L topramezone and 60 g/L cloquintocet-mexyl, as a suspo-emulsion (SE) formulation containing the new active constituent topramezone.

1.3 Proposed claims and use pattern

The proposed product Frequency Herbicide is intended for post-emergence weed control in wheat, barley and durum.

1.4 Mode of action

Topramezone is a highly selective herbicide, which controls a broad spectrum of grass and broadleaf weeds when applied post-emergence. It is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) in the biosynthesis of plastoquinone and indirectly of carotenoids. Chloroplast synthesis and function is disturbed. This leads to strong bleaching effects (by oxidative degradation of chlorophyll) particularly on the growing zones of the shoot in sensitive weeds. Concomitantly, growth is inhibited. Under the influence of light, chlorotic tissues become necrotic and plants usually die within 14 days after treatment. Topramezone is taken up via the root and shoot and is translocated in the plant both acropetally and basipetally.

Cloquintocet-mexyl is a herbicide safener used to improve cereal crop tolerance. Safeners are used extensively in cereals to protect crops from damage caused by selective herbicides without compromising weed control efficacy. The mechanism of safener action most widely accepted is that these chemicals enhance crop tolerance by inducing the expression of proteins involved in the metabolism of herbicides, thus accelerating their detoxification.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

Topramezone (pure substance, 99.8 per cent) is an odourless, white crystalline solid at room temperature, with a melting range of 220.9–222.2 °C. Topramezone (technical grade active ingredient (TGAI), 99.6 per cent) is a beige powdery fine—crystalline solid with a faint aromatic odour. Topramezone has a low vapour pressure of < 1 x 10–12 hPa at 20 °C and 25 °C, and there is no indication of sublimation up to the decomposition temperature of ~300 °C. The solubility of topramezone in deionized water was 510 mg/L and it reacts as a weak acid (pKa 4.06). Topramezone has no potential for bioaccumulation, as at pH 7 the log Pow is -1.52.

The APVMA has evaluated the chemistry (manufacturing process, quality control procedures, batch analysis, analytical methods, physio-chemical properties and spectroscopic data) and toxicological aspects of the active constituent topramezone and found them to be acceptable. The active constituent was approved on 27 July 2016 under the approval number 69090.

The active constituent topramezone is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of topramezone are listed below (Tables 1–2).

Table 1: Nomenclature and structural formula of the active constituent topramezone

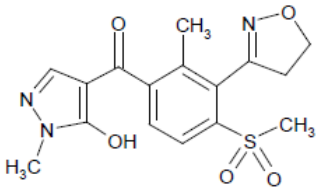
COMMON NAME (ISO):	Topramezone
IUPAC NAME:	[3-(4,5-dihydro-1,2-oxazol-3-yl)-4-(methanesulfonyl)-2-methylphenyl](5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone
CAS REGISTRY NUMBER:	210631-68-8
MOLECULAR FORMULA:	$C_{16}H_{17}N_3O_5S$
MOLECULAR WEIGHT:	363.39 g/mol
STRUCTURAL FORMULA:	

Table 2: Key physicochemical properties of the active constituent topramezone

PHYSICAL FORM:	White crystalline solid (pure substance, 99.8%) Beige powdery fine–crystalline solid (TGAI, 99.6% purity)
ODOUR:	Odourless (pure substance, 99.8%) Faint aromatic odour (TGAI, 99.6% purity)
MELTING RANGE:	220.9–222.2 °C (pure substance, 99.8%)
BOILING POINT:	Not measurable—decomposition above ~300 °C
RELATIVE DENSITY	1.411 (20 °C)
SURFACE TENSION:	69 mN/m (1.0% solution, 20 °C)
SOLUBILITY IN WATER:	510 mg/L in deionized water (pH 3.1, 20 °C) >100 g/L in alkaline medium (pH >9, 20 °C)
ORGANIC SOLVENT SOLUBILITY:	Acetone: 7 g/L Acetonitrile: 6.8 g/L Dichloromethane: 120 g/L Ethyl acetate: 3.8 g/L n-Heptane: <0.01 g/L Methanol: 1.8 g/L 1-Octanol: 0.4 g/L 2-Propanol: 0.2 g/L Toluene: 3.7 g/L All reported at 20 °C
DISSOCIATION CONSTANT (PK_A):	4.06 at 20 °C
OCTANOL/WATER PARTITION COEFFICIENT (LOG K_{OW}/K_{OW}):	-1.13 (unbuffered) -0.81 (pH 4) -1.52 (pH 7) -2.34 (pH 9) All reported as log Pow, at 20 °C
VAPOUR PRESSURE:	$<1 \times 10^{-12}$ hPa (20 °C and 25 °C)
HENRY'S LAW CONSTANT:	$<7.125 \times 10^{-14}$ $kPam^3mol^{-1}$ (20 °C)
STABILITY:	Stable for two years under ambient conditions Stable when stored at 54 °C for 14 days

HYDROLYSIS RATE:	Stable to hydrolysis in pH 4, 7 and 9 at 25 °C for 30 days and at 50 °C for 5 days in the absence of light
PHOTODEGREDATION:	Half-life of 72 days when ^{14}C-topramezone (Pyrazol label) was irradiated extensively for 30 days in natural water at 22 °C ^{14}C-Topramezone (Pyrazol label) was stable when irradiated extensively for 17 days in aqueous buffer solutions under sterile conditions at pH 5 and pH 9 at 22 °C
UV/VIS ABSORPTION SPECTRA:	ε = 27011 Lmol^{-1}cm^{-1} at 207 nm ε = 8601 Lmol^{-1}cm^{-1} at 272 nm ε = 5800 Lmol^{-1}cm^{-1} at 300 nm ε = 96 Lmol^{-1}cm^{-1} at 410 nm
FLAMMABILITY:	Not flammable
FLASH POINT:	Not applicable—solid at room temperatures
AUTO-FLAMMABILITY:	Not observed at temperatures up to 400 °C
EXPLOSIVE PROPERTIES:	Not explosive
OXIDIZING PROPERTIES:	Not oxidising
DANGEROUS GOODS CLASSIFICATION:	Not classified as a dangerous good

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

CONSTITUENT	SPECIFICATION	LEVEL
topramezone	topramezone	970 g/kg minimum

2.2 Formulated product

Frequency Herbicide is a suspo-emulsion (SE) formulation containing the new active constituent topramezone and the approved active constituent cloquintocet-mexyl, which is included as a herbicide safener. The product Frequency Herbicide will be manufactured overseas. The product will be packaged in 5 L to 1000 L fluorinated high denisty polyethylene (HDPE) or COEX (HDPE with barrier) containers. Tables three and four outline some key aspects of the formulation and physicochemical properties of the product. Suitable details of the product formulation, specifications for the ingredients, manufacture 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 for at least two years when stored under normal conditions in the proposed commercial packaging.

Table 3: Key aspects of the formulation of the product topramezone

DISTINGUISHING NAME:	Frequency Herbicide
FORMULATION TYPE:	Suspo-emulsion (SE)
ACTIVE CONSTITUENT CONCENTRATION/S:	Topramezone (60 g/L) and cloquintocet-mexyl (60 g/L)

Table 4: Physicochemical properties of the product topramezone

PHYSICAL FORM:	Light beige, liquid suspension
ODOUR	Moderate aromatic odour
PH:	4.0 (1% in pure water)
ACIDITY:	0.2% (calculated as H_2SO_4)
DENSITY:	1.033 g/m^3 at 20 °C
DYNAMIC VISCOSITY:	923 mPa.s (1 s^{-1}, 20 °C) 210 mPa.s (10 s^{-1}, 20 °C) 78 mPa.s (100 s^{-1}, 20 °C) 63 mPa.s (200 s^{-1}, 20 °C)
SURFACE TENSION	42.5 mN/m (0.1% in pure water, 20 °C) 41.6 mN/m (0.2% in pure water, 20 °C)
POURABILITY:	1.19% (w/w) poured residue 0.18% (w/w) rinsed residue after 1st rinse
DISPERSION STABILITY:	0.1% solution: 0 mL at 0.5 hr, completely redispersed at 24 hr, and 0 mL at 24.5 hr 0.2% solution: <0.04 mL at 0.5 hr, completely redispersed at 24 hr, and 0 mL at 24.5 hr
WET SIEVE TEST:	0.90% (75 µm sieve)
PERSISTENT FOAM:	0 mL after 0, 1, 3 and 12 min (0.1% and 0.2% solutions in pure water)
PARTICLE SIZE DISTRIBUTION:	d10% = 0.9 µm d50% = 1.8 µm d90% = 4.0 µm
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	Not oxidising

THERMAL STABILITY:	No exothermic decomposition up to 500 °C
FLASH POINT:	>88 °C
AUTO-FLAMMABILITY:	490 °C
FREEZING POINT:	-5.6 °C
CORROSIVE HAZARD:	Not corrosive to COEX (HDPE with barrier) containers
DANGEROUS GOODS CLASSIFICATION:	Not classified as a dangerous good
PACK SIZES:	5–1000 L
PACKAGING MATERIAL:	COEX (PE/PA) materials (HDPE with barrier) or fluorinated HDPE containers
STORAGE STABILITY:	The product is expected to remain within specifications for at least 2 years when stored under normal conditions in COEX (HDPE with barrier) and fluorinated HDPE containers

2.3 Recommendations

The APVMA Chemistry section has evaluated the chemistry of the active constituent topramezone and associated product Frequency Herbicide, including the manufacturing process, quality control procedures, stability, batch analysis results and analytical methods, and found them to be acceptable. The available storage stability data indicate that the formulated product is expected to remain stable for at least two years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details, the registration of Frequency Herbicide, is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

The toxicological data submitted on the active topramezone were considered sufficient to determine its toxicology profile and to characterise the risk to humans. The data included metabolism studies, acute toxicity studies (active constituent and product), short-term toxicity studies (oral and dermal), long-term oral toxicity studies (including carcinogenicity), reproductive and developmental toxicity studies, genotoxicity studies, neurotoxicity studies (acute and repeat-dose) and studies on metabolites and mode-of-action. Data were also submitted on the proposed product, Frequency Herbicide, containing topramezone and cloquintocet-mexyl.

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.

Chemical class

Topramezone is a member of the class of herbicides that inhibit the enzyme 4-hydroxyphenylpyruvate dioxygenase (4 HPPD), the second enzyme in the tyrosine catabolic pathway. In plants, inhibitors of 4 HPPD prevent carotenoid pigment formation, which in turn leads to chlorophyll degradation. In mammals, inhibition of 4 HPPD leads to increased serum levels of tyrosine, which may in turn have overt biological effects.

Cloquintocet-mexyl acts a safener, to prevent the phytotoxic action of an accompanying herbicide with which it is mixed. It has not been classified in a chemical class.

Pharmacokinetics

In rats, topramezone was rapidly (Tmax: one h) but only moderately (17–49 per cent) absorbed by the oral route. Tissue distribution of radioactivity was wide following oral dosing with ^{14}C labelled topramezone, with the highest concentrations found in organs involved in absorption/excretion (stomach, gut, kidney and liver), and the thyroid, ovaries, uterus and pancreas. The kidney, liver, thyroid and pancreas were target organs for toxicity in this species (rat). Following oral dosing, topramezone underwent minimal-moderate metabolism in rats and rabbits, with metabolism involving hydroxylation of the isoxazoline ring, followed by ring opening and removal of acetic acid; and hydrolysis at the methanone bridge. In rabbits only, one of the hydrolysis products underwent sulfation. In rats, elimination of test item-related material was primarily via the faeces (73–92 per cent; depending on dose), while both faecal and urinary routes were prominent excretion routes of test item-related material in rabbits (42.5 per cent and 51.5 per cent, respectively). Elimination was rapid in both species with the majority of test item-related material excreted in the first 24–48 h. Less than 1.3 per cent of the dose remained in the carcass after 168 h. Topramezone was not considered to be

bioaccumulative. Biliary excretion accounting for between nine and 30 per cent of the administered dose (decreasing with dose) was demonstrated in rats.

No dermal absorption studies were submitted. In a 28 day dermal toxicity study in rats, an increase in urine ketone levels, a pharmacological effect of the test item, was observed at all tested doses (≥100 mg/kg bw/d), suggesting a significant amount of the test item was absorbed via the dermal route.

Acute toxicity (active constituent)

Topramezone had low acute oral (LD_{50} >2000 mg/kg bw), dermal (LD_{50} >2000 mg/kg bw) and inhalational (LC_{50} >5050 mg/m^3) toxicity in rats. The test item was a slight skin and eye irritant in rabbits but was not a skin sensitiser in guinea pigs (Maximisation test).

Acute toxicity (product)

Based on submitted toxicological studies, the formulated product, Frequency Herbicide, containing 60 g/L topramezone and 60 g/L cloquintocet-mexyl has a very low toxicity via the oral (LD_{50} >2000 mg/kg bw) route of exposure and is of low toxicity via the dermal (LD_{50} >5000 mg/kg bw) and inhalation (LC_{50} >2835 mg/m^3) routes. The product is moderately irritating to rabbit skin and eyes, and is a skin sensitiser in mice (LLNA).

Repeat-dose toxicity

Repeat-dose toxicity studies (excluding carcinogenicity studies) by the oral route were conducted in mice (up to 90 days), rats (up to one year) and dogs (up to one year). A 28 day dermal toxicity study was also conducted in rats. Serum chemistry (all species) and urinalysis findings (rats and dogs; not assessed in mice) consistent with the pharmacological action of topramezone (4-HPPD inhibition) including elevated serum tyrosine levels and increased urinary ketone levels, such as 4-hydroxyphenyl pyruvic acid and other metabolites of tyrosine, were observed. Target organs for toxicity were the liver (mice and rats only), kidney (all species), thyroid gland (rats only), pancreas (rats only) and the eyes (rats only). Rats appeared to be the most sensitive species. The toxicity profile of topramezone (in repeat-dose toxicity studies) is similar to other 4-HPPD inhibitors, such as mesotrione.

In mice and rats, more so in the latter species, an increase in liver weights (absolute and/or relative to body weight), only occasionally with correlative histopathology findings (hepatocytic centrilobular hypertrophy and karyomegaly) was seen following topramezone treatment. Increased kidney weights (without any histopathological correlates) were seen in mice, rats and dogs. This was considered the result of an increased workload on the kidney involved in the elimination and excretion of test item-related material and/or increased urinary excretion of ketones.

The thyroid gland was a target organ for toxicity in rats but not mice or dogs. An increased incidence and/or severity of flaky colloid (characterised by flaky basophilic structures in the follicles) in the thyroid gland was observed in subchronic studies in rats (90 day studies, including the two generation reproductive study in rats), but not in the longer term studies. The flaky colloid findings were not considered to be associated with any of the other thyroid gland lesions and were not considered to be adverse; in longer term studies, the incidence of flaky colloid was high in all groups, including controls. In the one and two year studies in rats, there was an increased incidence of follicular cell hypertrophy and follicular cell hyperplasia, with an

increased incidence of thyroid gland tumours (follicular cell adenoma and carcinoma) seen in the carcinogenicity study. The reversibility of the non-neoplastic lesions was not assessed.

An increased incidence of diffuse degeneration of the pancreas was evident in treated rats only. The underlying cause of these lesions was unknown and hence the relevance to humans cannot be dismissed. Reversibility of this lesion was not assessed.

Corneal opacity, identified histopathologically as chronic keratitis, was seen in rats that had received topramezone. These ocular lesions were only observed after prolonged treatment to rats (studies of ≥ 90 days duration). No ocular lesions were seen in mice treated for up to 18 months or dogs treated for up to 12 months, though there were isolated incidences of cataracts (and lenticular degeneration) in treated animals in the three generation study in mice. Corneal opacity has been reported to occur in animals treated with other members of this pharmacological class. The corneal opacity has been suggested to be due to tyrosinaemia and not a direct test item-related effect. A mechanistic study demonstrated that corneal opacity in rats coincided with significant levels of tyrosine in the aqueous humour (levels were similar to serum levels). In this study, effects had largely reversed by the end of a six week recovery period, although serum and aqueous humour tyrosine concentrations had not yet returned to baseline. Similarly treated mice had elevated serum levels of tyrosine (associated with the pharmacology of the test item), but there were no corresponding ophthalmological findings (aqueous humour levels of tyrosine however were not measured). Serum tyrosine levels had returned to baseline within three weeks after cessation of dosing, despite the administration of higher doses. Rats had significantly higher serum tyrosine levels than mice at equivalent doses, suggesting species differences in either the formation or clearance of tyrosine, though a NOAEL for elevated serum tyrosine levels was not established in either species. Published data indicate that, compared with rats, mice have higher innate levels of hepatic tyrosine aminotransferase (TAT), the enzyme involved in tyrosine clearance. Generally, mice are considered to be a better animal model for tyrosine catabolism than rats. Estimated serum tyrosine levels at the chronic NOAEL for ocular lesions in mice (i.e. the highest tested dose, 8000 ppm; 1903/2467 mg/kg bw/d, M/F) was 190 µmol/L, while estimated serum tyrosine levels at the chronic NOAEL for ocular lesions in rats (6 ppm; 0.4/0.5 mg/kg bw/d, M/F) was 500–1000 µmol/L. These data indicate that serum tyrosine levels rather than dose levels are a better indicator for the risk of ocular lesions with topramezone treatment. The NOAEL for ocular lesions in rats (0.4/0.5 mg/kg bw/d, M/F), along with appropriate safety factors should be protective for the risk of ocular lesions in humans.

Chronic toxicity and carcinogenicity

Carcinogenicity studies were conducted in mice and rats. Treatment with topramezone in mice for 18 months did not induce an increase in any particular tumour type. However, in rats an increased incidence of thyroid gland tumours (follicular cell adenoma and carcinoma; both sexes) with an increased incidence of follicular cell hyperplasia was only observed in females. Follicular cell hypertrophy and hyperplasia were also observed in repeat-dose toxicity studies in rats, but not mice or dogs. Topramezone was determined to not be genotoxic, therefore, the increased incidence of thyroid tumours most likely has an underlying non-genotoxic mechanism. In mechanistic studies, rats that received topramezone had lower serum T4 levels than control animals. Persistent low levels of circulating thyroid hormones leads to a compensatory increased secretion of pituitary TSH. TSH stimulation of the thyroid gland leads to proliferative changes of follicular cells that include hypertrophy, hyperplasia, and eventually tumour formation. This is likely the underlying mechanism of thyroid tumour formation in rats given topramezone. A number of mechanistic studies were conducted to elucidate the cause of alterations to circulating thyroid hormone levels (assessing

whether topramezone affects thyroid hormone synthesis by inhibiting iodine incorporation in the thyroid gland or whether topramezone induces glucuronyltransferases that may be involved in thyroid hormone clearance). While the results were inconclusive, the findings of decreased serum T4 levels and, on occasion, elevated serum TSH levels in topramezone treated rats was sufficient evidence to suggest a TSH-mediated mechanism was the most likely mode of action for thyroid gland tumour formation in rats. In comparison with humans, rodents (particularly males) are more sensitive to perturbations of thyroid-pituitary hormone homeostasis and hence are more susceptible to thyroid cancers. Thyroid tumours in rodents that occur as a result of alterations to thyroid hormone levels are generally not considered to be relevant to human subjects. Therefore, topramezone was unlikely to pose a carcinogenic risk to human subjects.

Reproductive and developmental toxicity

Reproductive studies consisted of a two generation study in rats and a three generation study in mice. Fertility was unaffected by treatment; however, maternal treatment appeared to have some effects on pup parameters: reduced viability to PND4 (rats; possibly associated with maternal neglect), impaired pup weight gain during the lactation period (rats), an increased incidence of renal pelvic dilation (rats) and delayed preputial separation (both species). The underlying cause for delayed sexual maturation in males is unknown but may be secondary to lower pup weights (and delayed development).

Developmental toxicity studies were conducted in mice (one study), rats (two studies) and rabbits (10 studies). Placental transfer of topramezone was indicated in rabbits and elevated foetal serum levels of tyrosine were observed (either associated with pharmacological activity in the developing foetus or placental transfer of this amino acid). No adverse embryofoetal development effects were seen in mice. Similar foetal skeletal variations (delayed ossification and supernumerary ribs and/or vertebrae) were seen in rats and rabbits.

The incidence of skeletal variations appeared to correlate with maternal serum levels of tyrosine (supplementary dietary intake of this amino acid during treatment exacerbated the findings), suggesting an association with tyrosinaemia. These foetal variations have been observed with other members of this pharmacological class (eg mesotrione), none of which have been classified as reproductive/developmental toxicants. Furthermore, as noted previously, rats are particularly sensitive to 4-HPPD inhibitors, and NOAELs for these effects are considered to be protective of a possible effect in human subjects for risk assessment purposes.

An absent kidney/ureter was occasionally seen in rabbit foetuses following maternal exposure to topramezone. The incidence was: low but above the historical control data; not always observed with a dose relationship; and was not associated with maternal toxicity. There was no obvious correlation of the incidence of this malformation with a particular strain or particular colony of rabbit, with different batches of topramezone, or with maternal serum tyrosine levels. Other alterations observed in rabbits (malrotated limb, gastroschisis, acaudate, anal atresia, cleft palate, thoracoschisis) were only seen in a single study and their incidence above the historical control values is considered to be incidental and not associated with topramezone treatment.

Genotoxicity

Based on adequately conducted in vitro and in vivo studies, topramezone is not considered to have a genotoxic potential.

Neurotoxicity/immunotoxicity

There was no evidence of any neurotoxic effects in an acute toxicity study, three month repeat-dose toxicity study or a postnatal developmental study in rats.

Mode of action (toxicology)

Topramezone is an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase (4 HPPD), the second enzyme in the tyrosine catabolic pathway. In plants, inhibitors of 4 HPPD prevent carotenoid pigment formation, which in turn leads to chlorophyll degradation. In mammals, inhibition of 4 HPPD leads to increased serum levels of tyrosine, which may in turn have overt biological effects.

Chemicals with a similar mode of action include mesotrione, pyrasulfotole and isoxaflutole. The mode of action data indicated that topramezone treatment causes a perturbation of thyroid-pituitary hormone homeostasis, which is a potentially underlying cause for thyroid tumour formation in rats. Thyroid tumours in rodents that occur as a result of alterations to thyroid hormone levels are generally not considered to be relevant to human subjects. Therefore, topramezone is unlikely to pose a carcinogenic risk to human subjects.

Toxicity of metabolites and/or impurities

A number of toxicity studies were conducted with the metabolite, M670H05, which is generated by methanone bridge hydrolysis. In a four week repeat-dose toxicity study in rats, the only notable finding was an increase in serum tyrosine concentrations but only at high doses. This finding indicates the metabolite may have some pharmacological activity on 4-HPPD, albeit with lower potency than the parent compound. M670H05 was not genotoxic in vitro or in vivo. There were no direct adverse embryofoetal development effects in a developmental study in rats with M670H05. The only notable effects were secondary to maternotoxicity.

Reports related to human toxicity

There were no data or reports available for assessment by the APVMA related to accidental or intentional exposure of humans to topramezone.

3.2 Health-based guidance values and poisons scheduling

Poisons Standard

On 17 March 2016, the Delegate of the Secretary of Health published a final Scheduling decision to include topramezone in Schedule 5 of the Poisons Standard with no exemptions or concentration cut-offs. The

reasons for the Delegate's decision was based on the toxicity profile of topramezone that was consistent with criteria for listing in Schedule 5. The equivocal nature of the foetal developmental effects, including the apparently flat dose-response relationship and their possible relationship to the elevated tyrosine levels associated with treatment with this HPPD inhibitor, were considered insufficient to require listing in Schedule 6. An implementation date in the Poisons Standard was given as 1 June 2016.

Health-based guidance values

Acceptable Daily Intake (ADI)

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

Based on its mode of action and a comprehensive series of toxicological studies, the rat was identified as being the most sensitive laboratory animal species to topramezone treatment with corneal opacity (chronic keratitis), increased liver, kidney and thyroid weights, and histopathological lesions (including tumours) being observed. After considering all the toxicological data, an ADI of 0.004 mg/kg bw/d based on the NOAEL of 0.4 mg/kg bw/d from a two-year carcinogenicity study and using a 100-fold uncertainty (safety) factor was established. This ADI is supported by the NOAEL of 0.4 mg/kg bw/d in a two-generation reproductive study in rats and a NOAEL of 0.5 mg/kg bw/d in a developmental study in rabbits.

Acute Reference Dose (ARfD)

An ARfD is the estimate of the amount of a substance 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 one meal or during one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

Based on its mode of action and evidence from a comprehensive range of toxicological studies involving acute administration, it was considered unnecessary to establish an acute reference dose (ARfD) for topramezone.

3.3 Recommendations

Based on a review of the submitted toxicological data, the approval of topramezone and registration of Frequency Herbicide is supported from a human health perspective.

4 RESIDUES ASSESSMENT

Metabolism, analytical methodology, residue trial data, animal transfer and trade aspects have been considered for topramezone. For cloquintocet-mexyl which is also in Frequency Herbicide, the proposed use involves lower application rates than are currently approved and therefore residue or trade aspects of cloquintocet-mexyl will not be discussed further.

4.1 Metabolism

Maize

The metabolism of topramezone in maize has been studied following one single post emergent application of ^{14}C-labeled test materials applied at 0.15 kg ai/ha between crop growth stages BBCH 12 and 18.

The radioactive residue level in grain was low, at up to 0.11 mg equiv/kg with non-extractable residues accounting for >75.7 per cent of this TRR. Parent compound was ≤2.5 per cent TRR and M670H05 ≤3.4 per cent TRR. In forage (PHI 59–60 days) and straw intended as feedstuffs, parent was the main component, detected up to 41 per cent TRR (0.3 mg equiv/kg) with the free acid metabolite M670H05 at up to 7.2 per cent of the TRR (0.052 mg equiv/kg) in maize straw.

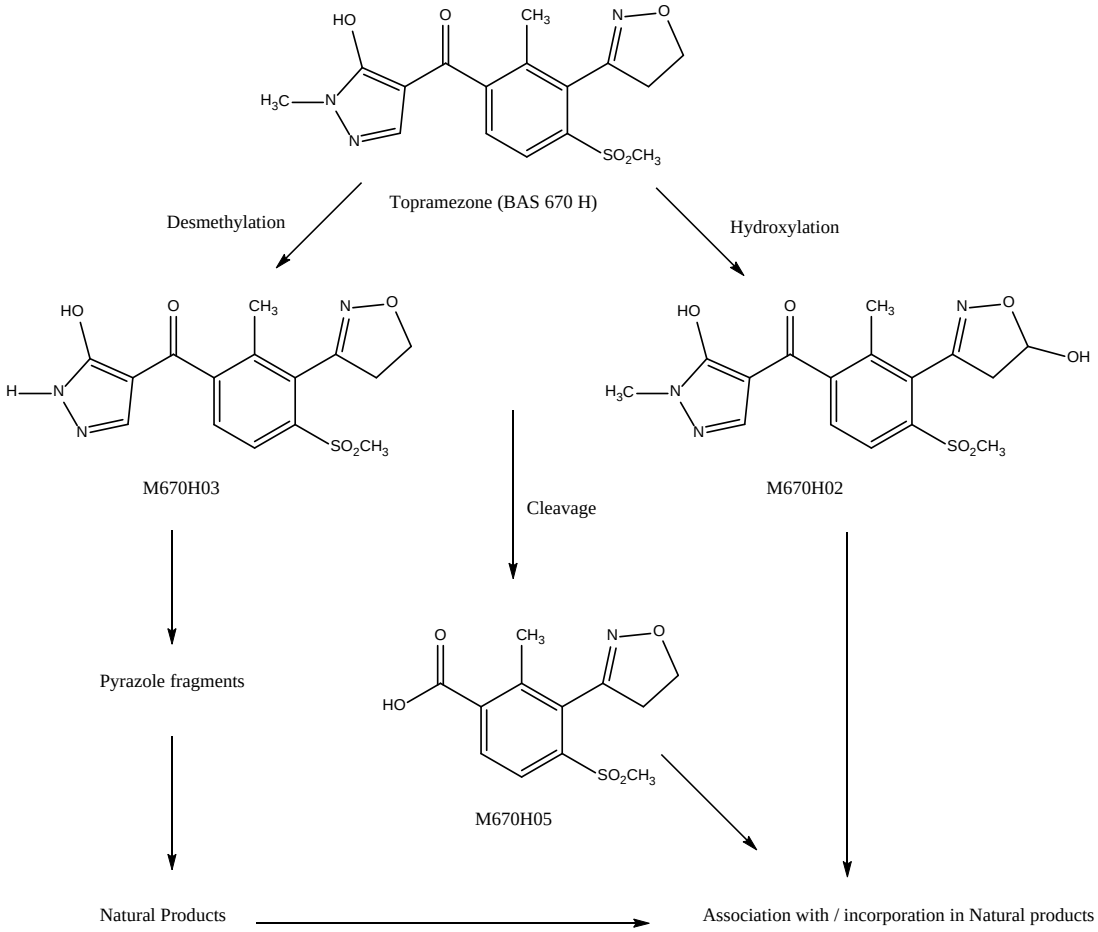
Confined Rotational Crops

The residues of topramezone in succeeding crops were investigated using a single application to bare sandy loam soil of ^{14}C-labeled test materials applied at 81–84 g ai/ha. Rotational crops were planted after aging periods of 34 days (radishes, winter wheat, and mustard greens), 99 days (sorghum and mustard greens) and 393 days (mustard greens), following simulation of ploughing by hand-tilling the plots to a depth of about 10 cm.

The residue level was only >0.01 mg equiv/kg in rotational crops from the 34 day after treatment (DAT) planting interval. There, the parent was observed as the major component (1.6–64.4 per cent TRR) in all edible crops (mustard green, wheat forage, hay, grain and straw) but ≤0.0047 mg equiv/kg in wheat grain, ≤0.0079 mg equiv/kg in mustard greens and 0.016 mg equiv/kg in wheat hay. The free acid metabolite M670H05 was observed at 10.3 per cent TRR in mustard greens (0.0026 mg equiv/kg) and 45 per cent of the TRR (0.0093 mg equiv/kg) in wheat grain. No significant residues were observed for longer DAT planting intervals.

The proposed metabolic pathway for topramezone in plants (maize) and rotational crops is summarised below:

Proposed metabolic pathway for topramezone in plants



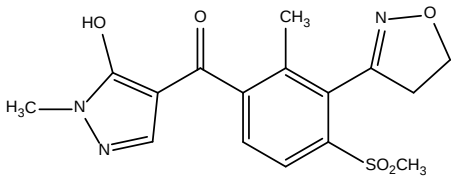
Lactating goats

Based on the daily consumption and the individual body weight, [^{14}C-phenyl]-BAS 670 H was administered daily for five consecutive days to two goats at a mean dose level of 9.9 mg/kg in the total ration (0.52mg/kg bw/d). Similarly, [^{14}C-pyrazole] -BAS 670 H was administered daily for five consecutive days to two goats at a dose level of 11.2 mg/kg in the total ration (0.51mg/kg bw/d). The goats were milked twice daily and samples were collected from the beginning of the acclimation until sacrifice. The goats were sacrificed 21–23 hours after administration of the fifth and final dose. Following sacrifice, composite sample of muscles, omental and perineal fats, liver and kidneys were taken for analysis.

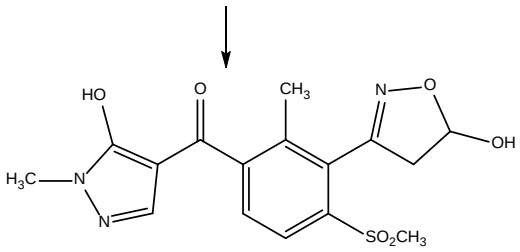
Up to 38 per cent of the total administered dose was excreted in faeces, with up to 45 per cent in urine. There was no indication of accumulation of topramezone residues in milk, muscle or fat where total radioactive residues were <0.01 mg equiv/kg. In offals, ^{14}C residues represented ≤0.36 mg equiv/kg and up to 2.2 mg equiv/kg in kidney and liver respectively. Unchanged parent and its hydroxylated metabolite (M670H02) were the main metabolites representing up to 79.5 per cent and 29.6 per cent TRR respectively. M670H01 was detected as a minor metabolite at <1 per cent TRR (0.013 mg equiv/kg).

The proposed metabolic pathway for topramezone in lactating goats is summarised below:

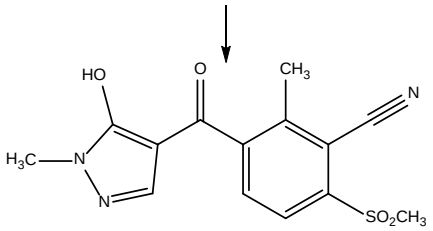
Proposed metabolic pathway for tropamezone in lactating goats



Topramezone (BAS 670 H)



M670H02



M670H01

Laying hens

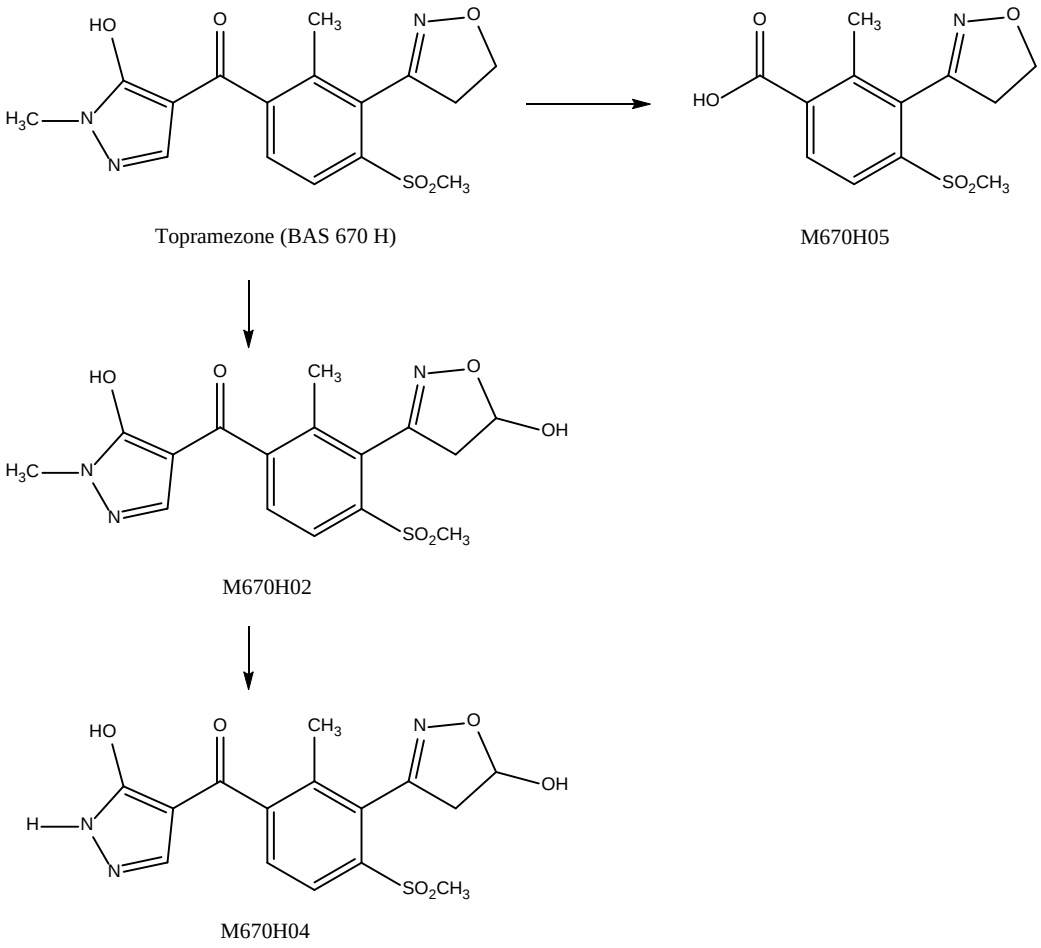
Based on the daily consumption and the individual body weight, [^{14}C-phenyl]-BAS 670 H was administered daily for 10 consecutive days to ten hens at the actual dose level of 13.4 mg/kg in the diet. Similarly, [^{14}C-pyrazole] -BAS 670 H was administered to ten hens at the actual dose level of 12.3 mg/kg in the diet.

Individual eggs were collected twice a day and pooled per treatment group. The hens were sacrificed 21–23 hours after administration of the tenth and final dose. After sacrifice, muscle (composite sample containing all breast and thigh muscle), fat (visceral fat and fat adhering to the skin and muscle), and entire liver were taken.

Up to 93 per cent of the total administered dose was found in excreta. In tissues and eggs, ^{14}C residues were <0.01 mg equiv/kg, but in liver they represented 1.68 mg equiv/kg (phenyl label). In liver, unchanged parent and its hydroxylated metabolite (M670H02) were the main metabolites representing up to 64.4 per cent and 29.9 per cent TRR respectively. The minor desmethyl hydroxyl metabolite (M670H04) was observed at up to 2.4 per cent TRR (0.04 mg equiv/kg).

The proposed metabolic pathway for topramezone in laying hens is summarised below:

Proposed metabolic pathway for topramezone in laying hens



Topramezone (BAS 670 H)

M670H05

M670H02

M670H04

4.2 Analytical methods and storage stability

In Australian wheat and barley trials topramezone and its metabolite M670H05 were extracted from the blended homogenous sample with water. An aliquot of the extract was filtered prior to analysis by reverse phase Ultra Performance Liquid Chromatography (UPLC) coupled with a tandem mass spectrometric detection (MS–MS). Quantitation was via external matrix standards. The LOQ for the method was 0.01 mg/kg for each analyte, the LOD was 0.003 mg/kg. Recoveries from fortified control samples were within acceptable limits.

Topramezone and its metabolite M670H02 were determined in liver, kidney, muscle, fat, milk and egg. The extraction was made with water; an aliquot was acidified and partitioned with dichloromethane and then in pH10 aqueous ammonium formate. The aqueous phase was injected directly in the LC/MS/MS system. Following limits of quantification were reached: 0.01 mg/kg in milk, muscle and egg, 0.05 mg/kg in liver, kidney and fat. Recoveries from fortified control samples were within acceptable limits. A second study to

validate the method for animal commodities, determined the LOQ to be 0.01 mg/kg for bovine liver, kidney, fat, muscle and chicken eggs and 0.001 mg/kg for milk. Recoveries from fortified control samples were within acceptable limits.

Storage stability

A storage stability study provided by the applicant indicated that both topramezone (BAS 670 H) and its metabolite M670H05 were stable in maize forage, grain and straw over a period of 26 months at -20ºC. In the Australian residue trials submitted, all samples were maintained under freezer conditions, prior to analysis and tested within eight months of collection. This is acceptable for the purposes of the current application.

4.3 Residue definition

Given parent was the major component in most commodities in the maize and rotational crop metabolism studies it is a suitable marker for enforcement and is also suitable for dietary exposure assessment. A residue definition of parent compound only is recommended for the proposed use in wheat, barley and durum for commodities of plant origin, in line with the definitions recommended overseas.

Parent topramezone was the predominant component in edible goat and hen matrices. Noting that quantifiable residues of M670H02 were not observed at the highest dose level (3.79 ppm) in a dairy cattle transfer study provided by the applicant and residue exposure to livestock and poultry is expected to be low (≤0.02 ppm), a residue definition of parent only is recommended for topramezone for commodities of animal origin for both enforcement and dietary risk assessment. This definition is line with those recommended overseas.

4.4 Crop residues & MRLs

The proposed use of Frequency Herbicide on wheat, barley and durum is for application at 12 g ai/ha topramezone + 12 g ai/ha cloquintocet-mexyl prior to crop stage Z32 (2-node stage). The proposed harvest withholding period is ‘Not required when used as directed’. The proposed grazing withholding period is six weeks.

Grain

Residues of topramezone in wheat (six) and barley (three) grain from Australian GLP trials involving application at 12 g ai/ha (1× proposed) at BBCH 23–31 were <LOD (<0.003, n=9) mg/kg (88–140 DAT). Residues were also <0.003 (nine) mg/kg after application at 2× the proposed rate.

In the supporting EU data on maize, residues in grain at harvest at 98–147 days after treatment at 2 58–74 g ai/ha (4.8–6.2× proposed) were <0.01 (12) mg/kg.

MRLs of *0.01 mg/kg are recommended for topramezone on GC 0654 Wheat (which will include durum wheat) and GC 0640 Barley, in conjunction with a harvest withholding period of ‘Not required when used as directed’.

Forage and straw

Residues of topramezone in wheat and barley forage at six weeks after application at 12 g ai/ha (1× proposed) were <0.003 (fresh weight, n = 7), 0.01 and 0.02 mg/kg (dry weight). It is noted that the residue detections were between the LOD and LOQ on a fresh weight basis. The OECD MRL calculator recommends an MRL of 0.03 mg/kg.

Residues of topramezone in wheat and barley straw from trials involving application at 12 g ai/ha (1× proposed) at BBCH 23–31 were <0.003 (fresh weight, n = 8) and 0.004 mg/kg (dry weight) (88–140 DAT).

As forage and straw showed similar residues, an MRL of 0.03 mg/kg is proposed for topramezone on Cereal forage and fodder. A grazing withholding period of 'Do not graze or cut for stock food for six weeks after application. When applying with a tank mix product, observe the grazing withholding period for the tank mix product if this is longer than six weeks' is supported noting bromoxynil products are included on the label as a tank mix product and some bromoxynil products have an eight week grazing withholding period.

4.5 Animal commodities & MRLs

Cereal forage and fodder can form 100 per cent of the diet for grazing livestock in Australia. The maximum livestock dietary exposure for cattle and sheep will be 0.02 ppm (HR in forage). Based on the dairy cattle animal transfer study and a dietary burden of 0.02 ppm, the required animal commodity MRLs for topramezone are estimated below:

Cattle

FEEDING LEVEL (PPM)	MILK	MUSCLE	LIVER	KIDNEY	FAT
	TOPRAMEZONE RESIDUE (MG/KG)				
0.36	<0.01	<0.01	0.608	0.188	<0.05
0.02–estimated burden	<0.01	<0.01	0.03	0.01	<0.05
Established MRLs	Not established	Not established	Not established		Not established
Recommended MRLs	*0.001	*0.01	0.05 (offal)		*0.01

Note: the milk MRL is recommended at the lowest validated LOQ, noting residues were not observed (<0.01 mg/kg) after dosing at up to 3.79 ppm.

Cereal grains can form 100 per cent of the diet for poultry in Australia. However, detectable residues of topramezone are not expected to occur in wheat and barley grain from the proposed use. Poultry commodity MRLs for topramezone will be established at the respective LOQs of the analytical method.

4.6 Crop rotation

Given the low residues observed in the confined crop rotation study (summarised in section 4.1) after application at much higher rates than proposed, it is not expected that residues of topramezone or its metabolites will occur in rotational crops planted after the primary crop.

4.7 Residues in animal commodities

The log P_{ow} for tropamezone is -1.13 (deionized water), -0.81 (buffer pH4), -1.52 (buffer pH7) indicates low potential for bioaccumulation.

4.8 Spray drift

The product will be applied by ground application only with a medium or larger spray droplet size.

In the topramezone dairy cattle transfer study provided in support of the application, dosing at 0.36 ppm give a maximum residue of 0.608 mg/kg in liver. The feeding level for residues in liver to be at the LOQ of 0.01 mg/kg is therefore 0.006 ppm. Assuming pasture consists of 3000 kg DM/ha this corresponds to an allowable drift of 0.018 g/ha or 0.0015× the field rate (12 g ai/ha).

Using the APVMA standard scenario for ground application / high boom / medium droplets, average spray drift deposition over a 100 metre field will drop below 0.0015× the field rate by 120 metres downwind from the application area. A no-spray zone for livestock areas of 120 meters is recommended for the protection of international trade in livestock commodities.

4.9 Dietary risk assessment

The chronic dietary exposure to topramezone 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 2011–12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for topramezone is equivalent to <5 per cent of the ADI.

HARVEST Modelling[2]: HARVEST Modelling of chronic dietary exposure is also performed on new chemicals. The HARVEST model estimated the chronic dietary exposure of topramezone as <5 per cent of the ADI for the general population.

It is concluded that the chronic dietary exposure to topramezone is acceptable.

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 2011–12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. An acute reference dose for topramezone was considered to be unnecessary. A NESTI calculation is not required.

[2].HARVEST is a computer dietary modelling program based upon statistical software that is used by FSANZ.

4.10 Recommendations

In considering the application, and section 5A(3)(b)(iii) of the schedule to the Code Act, the following amendments will be made to the APVMA MRL Standard should the application be approved:

Table 5: Amendments to the APVMA MRL Standard

AMENDMENTS TO TABLE 1			
COMPOUND		**FOOD**	**MRL (mg/kg)**
ADD:			
Topramezone			
GC	0640	Barley	*0.01
MO	0105	Edible offal (Mammalian)	0.05
PE	0112	Eggs	*0.01
MM	0095	Meat [mammalian]	*0.01
ML	0106	Milks	*0.001
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat	*0.01
GC	0654	Wheat	*0.01

AMENDMENTS TO TABLE 3	
COMPOUND	**RESIDUE**
ADD:	
Topramezone	Topramezone

AMENDMENTS TO TABLE 4		
COMPOUND	**ANIMAL FEED COMMODITY**	**MRL (mg/kg)**
ADD:		
Topramezone		
	Cereal forage and fodder	0.03

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 and main destinations

Wheat and barley are considered to be major export commodities[3], 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 Frequency Herbicide may have the potential to unduly prejudice trade.

Total exports of barley were 9,537 kilotonnes in 2016/17, valued at $2.43 billion. Total exports of wheat (including flour) were 22,057 kilotonnes in 2016/17, valued at $6.09 billion (ABARES). Major export destinations are summarised below:

COMMODITY	MAJOR DESTINATIONS
Barley	China, Japan, Korea, Vietnam, the Philippines, Taiwan, Saudi Arabia, Kuwait, United Arab Emirates
Wheat	Indonesia, India, Korea, China, Japan, Thailand, Malaysia, Philippines, Vietnam, Egypt, Nigeria, Yemen, Kuwait, New Zealand

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).

5.2 Overseas registrations and approved label instructions

The applicant indicated that topramezone products are registered for use on corn/maize in the USA, Canada, Europe, Argentina, Mexico, Chile and South Africa and on sugar cane in the USA.

5.3 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. Topramezone has not been considered by Codex.

The following relevant overseas MRLs have been established for topramezone:

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

Table 6: Proposed Australian and current international MRLs for Topramezone

COMMODITY	TOLERANCE FOR RESIDUES ARISING FROM THE USE OF TOPRAMEZONE (MG/KG)				
	AUSTRALIA (PROPOSED)	EU	JAPAN	CODEX	USA
Residue Definition	topramezone	topramezone	Not established	Not established	topramezone
Wheat	*0.01	*0.01			-
Barley	*0.01	*0.01			-
Edible offal (Mammalian)	0.05	0.2 (liver) 1 (kidney) *0.05 (other)			0.8 (Cattle, meat byproducts)
Meat [mammalian]	*0.01	*0.01 (muscle) *0.05 (fat)			-
Milks	*0.001	*0.01			-

MRLs for topramezone have also not been established in Korea or Taiwan

5.4 Potential risk to trade

Export of treated produce containing finite (measurable) residues of topramezone 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.

Quantifiable residues of topramezone are not expected to occur in wheat or barley grain. Noting finite residues may occur in liver and kidney following feeding on treated cereal forage and that some markets including Codex have not established MRLs, a 14 day ESI will ensure residues are <0.01 mg/kg in animal tissues for export. The risk to trade from the proposed use with respect to topramezone is low, however comment on the potential risk to trade is requested from stakeholders.

6 WORK HEALTH AND SAFETY ASSESSMENT

Frequency Herbicide is intended to be applied using ground boom for the control of various weeds in wheat, barley and durum. Frequency Herbicide is to be applied at a rate of 200 mL/ha in a minimum of 80 L/ha water, once a season.

6.1 Health hazards

Frequency Herbicide has a very low toxicity via the oral (LD_{50} >2000 mg/kg bw) route of exposure and is of low toxicity via the dermal (LD_{50} >5000 mg/kg bw) and inhalation (LC_{50} >2835 mg/m^3) routes but the product is moderately irritating to rabbit skin and eyes, and is a skin sensitiser.

6.2 Occupational exposure

Exposure during use

Users of the product may be exposed to the product during mixing and loading and application. In the absence of chemical-specific, worker exposure studies for Frequency Herbicide, the US EPA Pesticides Handlers Database (PHED, 1998) was used to estimate worker exposure during mixing, loading and application activities. Acceptable margins of exposure (MOE) for mixing, loading and application by ground boom (open cab) were obtained when users of the product wear appropriate personal protective equipment (PPE). Please see Safety Directions section below for the appropriate PPE.

Exposure during re-entry or rehandling

Farmers and farm workers may be exposed to the product when they re-enter treated areas for inspection and farming activities. In the absence of chemical-specific, worker exposure studies for Frequency Herbicide, the US EPA Occupational Pesticide Re-entry Exposure Calculator (OPREC, 2016) was used to estimate exposure during activities associated with re-entering treated areas. Acceptable MOEs were obtained from day 0 for scouting and hand weeding activities.

6.3 Recommendations

Frequency Herbicide, a suspo-emulsion (SE) formulation containing 60g/L topramezone and 60 g/L cloquintocet-mexyl for the control of various weeds in cereals, is supported from a human health perspective. Frequency Herbicide can be used safely if used in accordance with the instructions and the following first aid instructions, safety directions and re-entry statements that are recommended for the product label.

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26; New Zealand 0800 764 766. If swallowed, do NOT induce vomiting.

Safety directions

Harmful if inhaled. Will irritate the eyes and skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. Do not inhale vapour. If product on skin immediately wash area with soap and water. If product in eyes, wash it out immediately with water. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow length chemical resistant gloves and face shield or goggles. If applying by boomspray equipment (open cab) wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). Wash hands after use. After each day use, wash gloves, face shield or goggles and contaminated clothing.

Precautionary (warning) statements

Do not allow entry into treated areas until spray has dried. If prior entry is necessary wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

7 ENVIRONMENTAL ASSESSMENT

In considering the environmental safety of the proposed use of Frequency Herbicide, the APVMA had regard to the toxicity of the active constituent and its residues, including metabolites and degradation products, in relation to relevant organisms and ecosystems. A comprehensive environmental data package has been submitted for topramezone and a full risk characterisation was conducted. The reported endpoints for the proposed formulation include the contribution from cloquintocet-mexyl (ie formulation endpoints are reported in terms of total active constituents or 'acs').

7.1 Fate and behaviour in the environment

Soil

Topramezone and its metabolite M670H05, 3-(4,5-dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methyl-benzoic acid, were determined to be the relevant residues in soil. Metabolite M670H05 was formed in laboratory aerobic degradation studies up to 19 per cent, and it was detected in all field soil dissipation studies up to 38 per cent.

Photodegradation is not expected to be an important process in the degradation of topramezone in soil. No significant differences were observed between the irradiated and the dark control samples in laboratory trials.

The degradation of topramezone in soil is mainly a biological process under aerobic conditions. The primary step is an oxidative attack of the carbonyl group, which results in the formation of the metabolite M670H05. The mineralization of topramezone is low to moderate (up to 11 per cent AR after 120 days), with bound residues formed in moderate amounts (up to 36 per cent AR after 120 days) which were mainly associated to the fulvic acid fraction. Degradation of topramezone is slow and usually follows bi-phasic kinetics with non-normalised DT_{50} values ranging 85–357 days (six laboratory soils) and 11–69 days (seven European field sites). A soil DT_{50} of 77 days for topramezone was determined to be the key regulatory endpoint for risk assessment, which was based on the geometric mean of five field values (slow phase of DFOP kinetics) normalised to standard conditions (20°C, pF2).

Under anaerobic conditions, the mineralisation of topramezone is negligible and large amounts of bound residues are formed (up to 72 per cent AR) which are mainly associated to humin. The dissipation of topramezone followed first order kinetics under anaerobic conditions with DT_{50} values ranging 22–28 days (two laboratory soils) which is mainly due to formation of bound residues rather than biodegradation.

Adsorption of topramezone to soil is moderate with $K_{f,oc}$ values ranging 15–297 L/kg (14 soils). Supplementary measurements at only one concentration on six other soil samples, gave K_d values which are in line with these K_f values. A pH dependence was observed in a sigmoidal function with adsorption increasing when pH decreases. A K_d of 0.33 L/kg for topramezone was determined to be the key regulatory endpoint for risk assessment, which was the predicted value for one per cent OC based on regression of K_f and K_d values of 12 soils with pH >6.7.

The leaching behaviour of topramezone was studied at two field sites in Germany, from May 2000 to May 2005. Following applications of 75 g ac/ha or 2× 50 g ac/ha (one year apart), topramezone was detected in the groundwater at only few sampling dates, with measured mean concentrations over the entire field never exceeding 0.061 µg ac/L; but some concentrations higher than 0.10 µg ac/L were occasionally measured in individual wells. Considering the low application rate of topramezone in Australia (12 g ac/ha) and low occurrence of detections in groundwater in the field leaching trials, the risk of contaminating groundwater is considered to be low.

The dissipation of the metabolite M670H05 in soil followed first-order kinetics with DT_{50} values of 54 days (one aerobic laboratory soil) and 25–75 days (seven European field sites). When normalised to standard conditions (20°C, pF2), the geometric mean of five field DT_{50} values was 29 days. The adsorption of metabolite M670H05 to soil is extremely low, nearly 0 in some soils. In the field leaching studies, it was detected more frequently in the groundwater than topramezone; the mean concentrations were mostly lower than 0.10 µg/L but some individual samples measured up to 0.43 µg/L. Considering the low application rate of topramezone in Australia (12 g ac/ha) relative to the rates tested in the field leaching studies, the risk of metabolite M670H05 contaminating is considered to be low.

Water

Topramezone and its metabolites M670H05 and M670H01, [3-cyano-4-methanesulfonyl-2-methylphenyl]-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-methanone, were determined to be the relevant residues in aquatic systems. Metabolite M670H05 and M670H01 could be formed in significant amounts in water, depending on the conditions. M670H05 formed up to 51 per cent in water under outdoor conditions, and M670H01 formed up to 10 per cent in sediment under dark conditions.

Topramezone is hydrolytically stable. When exposed to the light, topramezone was stable in sterile buffer solution but showed a slow degradation in a sample of ‘natural water’, which indicate that some dissolved photosensitizers might enhance the degradation in water.

In two water-sediment degradation systems under dark aerobic conditions, the dissipation of topramezone from water was mainly by transfer to the sediment and formation of bound residues. Up to 39 per cent of applied topramezone partitioned to sediment, with the amount of bound residues (ranging 10–79 per cent AR) being highly dependent on the clay and organic carbon content. Mineralization is low (<1.5 per cent AR) with M670H01 being the only major metabolite up to 10 per cent in the sediment of high clay and organic carbon content. The geometric mean DT_{50} values for topramezone under dark laboratory conditions were 9.5 days in the water phase (first-order kinetics), 52 days in the sediment (first-order kinetics), and 78 days in the whole system (slow phase of bi-phasic kinetic model). The whole system DT_{50} of 78 days for topramezone was determined to be the key regulatory endpoint for risk assessment. A DT_{50} of 180 days was determined for metabolite M670H01 in the water phase.

A complementary water-sediment study was performed under outdoor conditions, with the natural variations of light and temperature from August to November in Germany. The metabolite M670H01 was formed in minor amounts, but high amounts of M670H05 were formed up to 51 per cent. The results clearly indicate that the photodegradation of the active substance in water is likely, resulting in significant amounts of acid metabolite. The DT_{50} values of topramezone under outdoor conditions were 62 days in the water phase (geomean of two radiolabels based on slow phase), 179 days in the sediment (phenyl radiolabel, first-order),

and 79 days in the whole system (geomean of two radiolabels, first-order). The DT_{50} value for metabolite M670H05 was 180 days in the water phase (first-order kinetics).

Air

After 24 hours, less than two per cent of topramezone volatilised from treated soil or plant surfaces. Considering these experimental results, its low vapour pressure (1×10^{-10} Pa at 20°C), and rapid predicted rate of photochemical oxidative degradation (DT_{50} < 1.1 days), it was concluded that the risk of topramezone entering or being transported in the air is very low.

7.2 Effects and associated risks to non-target species

Terrestrial vertebrates

Topramezone is of low toxicity to birds (LD_{50} >2000 mg ac/kg bw) and mammals (LD_{50} >2000 mg ac/kg bw). Following long-term exposure in birds, reduced 'hatched chicks of fertile eggs' and increased 'dead-in-shell fertile eggs' at 70 mg ac/kg bw/d was observed at 70 mg ac/kg bw/d (NOEL 19 mg ac/kg bw/d). Following long-term exposure in mammals, increased eye and kidney lesions was observed at 4.0 mg ac/kg bw/d in parents in the rat reproduction study (NOAEL 0.40 mg ac/kg bw/d) and on relevant substance related effects at 3.9 mg ac/kg bw/d in the 12–month feeding study in rat, and 3.6 mg ac/kg bw/d in the 24–month feeding study in the rat. The NOAEL of 0.40 mg ac/kg bw/day is not specific to rat and would cover the NOAEL/LOAEL determined to be 0.5/1.5 mg ac/kg bw/d in the rabbit based on effects in nine developmental toxicity studies. Overall, the NOAEL of 0.40 mg ac/kg bw/d is considered relevant for ecotoxicology and is used in the mammalian risk assessment.

The major potential routes of exposure of terrestrial vertebrates to topramezone are considered to be feeding on food items (eg vegetation and invertebrates) directly contaminated from spray application of the product. Maximum predicted dietary dosages of topramezone did not exceed regulatory acceptable doses assuming treated vegetation comprised 100 per cent of their diets. Therefore, risks of topramezone to terrestrial vertebrates were considered to be acceptable under the proposed conditions of use.

Aquatic species

Topramezone is of low toxicity to fish (LC_{50} >100 mg ac/L) and aquatic invertebrates (EC_{50} >100 mg ac/L). The formulated SE product containing cloquintocet-mexyl was more toxic to aquatic invertebrates with an EC_{50} 0.36 mg acs/L. Algae were similarly more sensitive to the formulated SE product containing cloquintocet-mexyl (E_rC_{50} 0.65 mg acs/L) than to technical topramezone (E_rC_{50} 68 mg acs/L). Following long-term exposure to topramezone, reduced body weight and length was observed in fish at 10 mg ac/L (NOEC 3.2 mg ac/L) and a reduction in number of offspring was observed in aquatic invertebrates at 100 mg ac/L(NOEC 50 mg ac/L). Aquatic plants were clearly the most sensitive aquatic organisms with E_rC_{50} values of 0.063 mg ac/L for topramezone and 0.093 mg acs/L for the formulated SE product containing cloquintocet-mexyl.

Aquatic toxicity data on the metabolites M670H01 and M67H05 for a number of species demonstrate that the metabolites are less toxic than the parent substance topramezone. Notably for the sensitive aquatic plant,

M670H01 is four-fold less toxic and M670H05 is 40-fold less toxic. Considering maximum formation fractions (10 per cent and 51 per cent, respectively) and low relative toxicity, the metabolites are not of ecological concern in aquatic systems.

The major potential routes of exposure of aquatic species to topramezone are considered to be spray drift or runoff from the treatment area. Inhibition of growth of aquatic plants was determined to be the effect of greatest concern in aquatic systems. Runoff risks of topramezone were determined to be acceptable when considering dilution in the catchment, and standard precautionary measured are required to minimise risks of runoff. A mandatory no-spray zone is not required to address spray drift risks to aquatic species when using ground application equipment.

Bees and other non-target arthropods

Topramezone is considered to be non-toxic to bees (oral LD_{50} >72 µg ac/bee; contact LD_{50} >100 µg ac/bee). No mortality was observed in any of the tested concentrations. Exposure of bee larvae is expected to be negligible because topramezone is a herbicide and cereal crops are not attractive to bees (wind-pollinated). Therefore, risks of topramezone to bees are considered to be acceptable under the proposed conditions of use.

Other beneficial (predatory and parasitic) arthropods could be directly exposed to topramezone within the crop during treatment or as a result of spray drift. In tier one (glass plate) laboratory tests, an SC formulation (+ adjuvant) without a safener was not toxic to parasitic arthropods (LR_{50} >100 g ac/ha), while an LR_{50} 105 g ac/ha was established for predatory arthropods. Assuming non-target arthropods are exposed to fresh-dried residues within the treatment area immediately after application, risks of topramezone to beneficial arthropods were determined to be acceptable.

Soil organisms

Topramezone did not exhibit intrinsic acute toxicity to soil macro-organisms such as earthworms (LC_{50} >1000 mg ac/kg dry soil). Following long-term exposure, reduced adult survival and reproduction was observed in other soil macro-organisms, such as collembolans, at concentrations as low as 74 mg ac/kg dry soil (NOEC 37 mg ac/kg bw). No adverse effects were observed on soil respiration or nitrification processes up to 0.67 mg ac/kg bw/d, the highest concentration tested. Assuming no interception and incorporation into the top five cm, maximum predicted soil concentrations of topramezone did not exceed regulatory acceptable concentrations. Therefore, risks of topramezone to soil organisms were considered to be acceptable under the proposed conditions of use.

Non-target terrestrial plants

Non-target terrestrial plants adjacent to the treatment area could be directly exposed to spray drift during treatment. Following post-emergent exposure in vegetative vigour tests, non-target terrestrial plants were not sensitive to the proposed SE formulation containing cloquintocet-mexyl with ER_{25} and ER_{50} values >12 g acs/ha. Based on the available information, it appears the presence of the safener cloquintocet-mexyl also reduces the toxicity of topramezone to non-target plant species. The post-emergent toxicity of an SC formulation (+ adjuvant) without a safener was further examined under field conditions for four sensitive non-target terrestrial plant species. Toxicity values derived from the field tests were higher than those derived in

greenhouse trials by a factor of at least two, with pea being the most sensitive species tested (ER_{25} 19 g acs/ha, ER_{50} 26 g acs/ha). The pea endpoints from the field trials were considered to be appropriate regulatory endpoints considering the maximum rates tested in the greenhouse tests with SE product containing cloquintocet-mexyl did not exceed 12 g acs/ha for the most sensitive species.

The metabolite M670H05 is likely to be present in the soil under field conditions; however, it is not of concern since it is less toxic than topramezone on a sensitive species by at least one order of magnitude (aquatic plants). The metabolite M670H01 is toxic to aquatic plants by less than one order of magnitude compared to topramezone; however, is only detected in prolonged anaerobic conditions which are unlikely to occur for the intended use of topramezone.

Pre-emergent (seedling emergence) toxicity data indicated that some species are sensitive to soil residues from the proposed SE formulation with cloquintocet-mexyl. Sugarbeet was the most sensitive species tested with an ER_{25} value of 2.1 g acs/ha and an ER_{50} value of 5.6 g acs/ha. Pre-emergent exposure to combined residues of cloquintocet-mexyl and topramezone was determined to be of greatest concern for non-target terrestrial plants. When applied in combination with bromoxynil, mandatory no-spray zones of 10 metres was determined to be appropriate. When applied in combination with MCPA, mandatory no-spray zones of 20 metres was determined to be appropriate.

7.3 Recommendations

Based on the outcome of the risk assessment, the APVMA is satisfied that the use of the product meets the safety criteria with respect to environmental considerations. Standard precautionary measures are required to minimise risks of runoff, and mandatory no-spray zones are required for the protection of aquatic and terrestrial environments.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

The proposed product Frequency Herbicide containing 60 g/L topramezone and 60 g/L cloquintocet-mexyl (crop safener), is intended for post-emergence weed control in winter wheat, barley and durum.

Trial data were assessed for a range of common weed species, crop safety for wheat, barley and durum, crop plantback safety and plantback periods on wheat, barley and durum and a range of other crops.

8.2 Efficacy and target crop/animal safety

Efficacy

Efficacy was assessed on wild radish*, Raphanus raphanistrum*, bindweed, *Polygonum convolvulus, w*ireweed, *(Polygonum aviculare),* Capeweed , *(Arctotheca calendula),* turnip weed, *(Rapistrum rugosum),* sowthistle, (*Sonchus oleraceus),* deadnettle, *(Lamium amplexicaule),* fleabane, *(Conyza bonariensis),* fumitory, *(Fumitory spp), s*carlet pimpernel, *(Anagallis coerulea), s*hepherds purse, *(Capsella bursa-pastoris),* subterranean clover, *(Trifolium subterraneum), c*ommon vetch, *(Vicia sativa)*, bifora, *(Bifora testiculata)*, stinging nettle, *(Urtica urens),* wild oats *(Avena fatua and Avena sterilis)* and Charlock, *(Sinapsis arvensis).*

Frequency Herbicide was applied at the label rate of 200 mL/ha alone, and in combination with bromoxynil at 1050 and 1200 mL/ha with adjuvant, to assess efficacy and crop safety on wheat, barley and durum. Crop safety was also assessed at double label rates of 400 mL/ha plus bromoxynil at up to 2400 mL/ha.

Efficacy was assessed by percentage control and crop safety by crop establishment, crop phytotoxicity, crop biomass and crop yield. Plantback safety and re-cropping times were also assessed on multiple cultivars of wheat, barley, canola, chickpea, field pea, lupin, lentil, cotton, maize, mungbean, sorghum, sunflower and safflower. Plantback and suitable re-cropping intervals were assessed by crop establishment, crop phytotoxicity and crop biomass.

Frequency Herbicide applied alone at the proposed label rate resulted in 75.2 per cent control of wild radish at 36 to 58 days after treatment, and 94.6 per cent control when applied at the label rate plus 1200 mL/ha bromoxynil. Frequency Herbicide applied alone at the proposed label rate, resulted in 92.0 per cent control of sowthistle at 39 to 48 days after treatment, and 98.9 per cent control when applied at the label rate plus 1200 mL/ha bromoxynil.

In all efficacy trials, Frequency Herbicide, tank mixed with 1200 mL/ha bromoxynil, provided commercial control (90 to 100 per cent) of all weeds evaluated. Frequency Herbicide applied at the proposed label rate tank-mixed with 1200 ml/ha bromoxynil, resulted in 55 per cent control of wild oats at six weeks after treatment and seed set was reduced by 60 per cent compared to the untreated control.

Assessment of phytotoxicity showed a mean percentage of 0.066 per cent on wheat at about 40 days after treatment with Frequency Herbicide applied alone at the proposed label rate. When applied at double the label rate, the percentage was 0.58 per cent, and 0.38 per cent when applied at the label rate plus the

recommended rate of bromoxynil. Phytotoxicity results on durum were similar to wheat. There was no significant phytotoxicity recorded on barley in multiple trials. In terms of biomass and yield, there was no significant reduction in wheat, barley or durum, when Frequency Herbicide was applied alone at label and double label rates, or tank mixed with bromoxynil at the recommended rate.

Re-cropping and plantback trials indicated that Frequency Herbicide was safe to a range of crops when the recommended label interval for plantback was followed. Trial data supported a six week plantback interval for wheat, barley and durum and a four month plantback interval for crops other than wheat, barley and durum.

8.3 Recommendations

The APVMA is satisfied that data from trials supporting the efficacy and crop safety of the product adequately demonstrate that if used according to the product label directions, the product is effective for its proposed uses, and safe to host crops.

9 LABELLING REQUIREMENTS

CAUTION

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

FREQUENCY® HERBICIDE

ACTIVE CONSTITUENT: 60 g/L TOPRAMEZONE
60 g/L CLOQUINTOCET-MEXYL
SOLVENT: 320 g/L LIQUID HYDROCARBONS

GROUP **H** HERBICIDE

For the control of certain broadleaved weeds including wild radish and suppression of wild oats in winter cereals as indicated in the Directions for Use table.

IMPORTANT: READ THIS LEAFLET BEFORE USING THIS PRODUCT

CONTENTS: 5L, 10L, 15L, 20L, 110L, 1000L

BASF Australia Ltd ABN 62 008 437 867
Level 12, 28 Freshwater Place Southbank VICTORIA 3006

® Registered trademark of BASF

APVMA Approval No.: 86267/115160

DIRECTIONS FOR USE

RESTRAINTS
DO NOT apply by aircraft
DO NOT apply after the 2-node stage (Z32)
DO NOT apply to crops that are stressed through disease, insect damage, frost, nutrient deficiencies, other herbicide use, excessively moist or dry conditions, or inappropriate soil type
DO NOT apply if rain is expected within 2 hours
DO NOT apply more than 1 application per season.
DO NOT apply if heavy rains or storms are forecast within 3 days.
DO NOT irrigate to the point of runoff for at least 3 days after application.

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

NO-SPRAY ZONE FOR PROTECTION OF INTERNATIONAL TRADE
DO NOT apply if there are livestock, pasture or any land that is producing feed for livestock within 120 metres downwind from the application area.

NO-SPRAY ZONES FOR PROTECTION OF THE TERRESTRIAL ENVIRONMENT
DO NOT apply if there are sensitive crops, gardens, landscaping vegetation, protected native vegetation or protected animal habitat within 10 metres (when tank mixed with bromoxynil) or 20 metres (when tank mixed with MCPA) downwind from the application area.

CROP	WEEDS	WEED STAGE	RATE	CRITICAL COMMENTS
Wheat Barley Durum	Wild radish (*Raphanus raphanistrum*)	Up to the 6-leaf stage	200 mL/ha + 900 mL/ha to 1.2 L/ha Bromicide®* 200 Selective Herbicide (200 g/L bromoxynil product) + 1% Hasten or similar MSO adjuvant	Apply to actively growing weeds, free from stress. Use the higher rate of bromoxynil under high populations and where conditions are less than ideal such as climatic stress or plant shading. Apply to crops from the 2-leaf stage (Z12) but prior to the 2-node stage (Z32). Transient bleaching of the crop may occur, particularly under cold or frosty conditions and can be exacerbated in northern areas where frost/cold starts followed by warm bright sunlight days follow. Trial data has shown that under these conditions final yield will not be impacted.
	Bifora (*Bifora testiculata*), Bindweed/buckwheat (*Fallopia convolvulus*), Capeweed (*Arctotheca calendula*), Charlock (*Sinapsis avensis),* Deadnettle (*Lamium amplexicale*), Fleabane (*Conyza* spp.), Fumitory (*Fumaria* spp.), Pimpernel (*Anagallis arvesnsis*), Shepherd's purse (*Capsella bursa-pastoris*), Sow thistle/milk thistle (*Sonchus oleracheus*), Stinging nettle (*Urtica dioica*), Subterranean Clover (*Trifolium subterraneum*), Tares (*Vicia sativa*), Turnip weed (*Rapistrum rogosum*), Wireweed (*Polygonum avicluare*)	Up to the 6-leaf stage	200 mL/ha + 900 mL/ha to 1.2 L/ha Bromicide®* 200 Selective Herbicide (200 g/L bromoxynil product) + 1% Hasten or similar MSO adjuvant	Use the higher rate of bromoxynil under high populations and where conditions are less than ideal such as climatic stress or plant shading. Apply to actively growing weeds, free from stress. Apply to crops from the 2-leaf stage (Z12) but prior to the 2-node stage (Z32). Transient bleaching of the crop may occur, particularly under cold or frosty conditions and can be exacerbated in northern areas where frost/cold starts followed by warm bright sunlight days follow. Trial data has shown that under these conditions final yield will not be impacted.

CROP	WEEDS	WEED STAGE	RATE	CRITICAL COMMENTS
Wheat Barley Durum	Deadnettle (Lamium amplexicale), Fumitory (*Fumaria* spp.), Shepherd's purse (*Capsella bursa-pastoris*), Sow thistle/milkthistle (*Sonchus oleracheus*), Stinging nettle (*Urtica urens*), Turnip weed (*Rapistrum rogosum*), Wild radish (*Raphanus raphanistrum*), Wireweed (*Polygonum avicluare*)	Up to the 6-leaf stage	200 mL/ha + 440 mL to 600 mL/ha Polo®* 570 LVE Herbicide (570 g/L L.V.E MCPA product) + 1% Hasten or similar MSO adjuvant	Apply to actively growing weeds, free from stress. Use the higher rate of MCPA LVE under high populations and where conditions are less than ideal such as climatic stress or plant shading. Apply to crops from the 3-leaf stage (Z13) but prior to the 2-node stage (Z32). Transient bleaching of the crop may occur, particularly under cold or frosty conditions and can be exacerbated in northern areas where frost/cold starts followed by warm bright sunlight days follow. Trial data has shown that under these conditions final yield will not be impacted.
Wheat Barley Durum	Suppression of seed set in wild oats in northern NSW and Qld cropping zones where *Avena sterilis* is dominant in targeted population	From 2 leaf to 2 tillers (GS 12- 22)	200 mL/ha + 900 mL/ha to 1.2 L/ha Bromicide®* 200 Selective Herbicide (200 g/L bromoxynil product) + 1% Hasten or similar MSO adjuvant	Frequency® Herbicide will provide useful suppression of seed set in wild oats. Apply to actively growing weeds, free from stress. Apply to crops from the 2-leaf stage (Z12) but prior to the 2-node stage (Z32). Significant bleaching and reduction of growth of wild oats will occur, resulting in death of some plants and a significant reduction in flowering and seed set of surviving plants, however complete control of wild oats may not be seen. Trials have shown that consistency of seed set reduction on wild oats in southern regions where *Avena Fatua* is dominant have has been greatly reduced compared to fields in the northern cropping area where *Avena sterilis* is dominant. Where wild oats are a major target either a split application or tank mix with a compatible wild oat control product is recommended Transient bleaching of the crop may occur, particularly under cold or frosty conditions and can be exacerbated in northern areas where frost/cold starts followed by warm bright sunlight days follow. Trial data has shown that under these conditions final yield will not be impacted.

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

WITHHOLDING PERIOD
HARVEST: NOT REQUIRED WHEN USED AS DIRECTED

GRAZING: DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 6 WEEKS AFTER APPLICATION. WHEN APPLYING WITH A TANK MIX PRODUCT, OBSERVE THE GRAZING WITHHOLDING PERIOD FOR THE TANK MIX PRODUCT IF THIS IS LONGER THAN 6 WEEKS
EXPORT SLAUGHTER INTERVAL (ESI) 14 DAYS
Livestock that has grazed on or been fed treated crops should be placed on clean feed for 14 days prior to slaughter.

GENERAL INSTRUCTIONS
FREQUENCY® Herbicide is a post-emergence, contact foliar-absorbed herbicide and will not control weeds which emerge after application. FREQUENCY® Herbicide will provide rapid bleaching of the target weeds. When mixed with bromoxynil according to the label, this additional activity will lead to rapid burning of target weeds. Both FREQUENCY® Herbicide and bromoxynil are light activated herbicides. Faster and more completed activity will be seen in higher light conditions. Due to the contact nature of FREQUENCY® Herbicide applications early in the season where better coverage is possible will result in better control. In some instances, complete control of weeds may not be seen, however a significant reduction in biomass will be observed and weeds will likely be uncompetitive with the crop.

To ensure thorough weed coverage, FREQUENCY® Herbicide should be applied in a minimum of 80L/ha water.

MIXING
Half fill the spray tank with clean water. Commence agitation and add the required amount of product to the tank. Maintain agitation whilst filling the tank and throughout the spraying operation.

FREQUENCY® Herbicide is a suspo-emulsion formulation. When using in a tank mix with other herbicides the following mix order should be observed;

1. half fill the spray tank;
2. add any granule (WG) formulated products first and allow dispersion, followed by any suspension concentrates (SC/flowable);
3. add any water-soluble salts;
4. add FREQUENCY® Herbicide and any EC formulations;
5. add any adjuvants as recommended.

Adjuvants
FREQUENCY® Herbicide requires the use of an MSO type adjuvant such as Hasten to allow better uptake into the target weed for full efficacy. Use of non-ionic surfactants and mineral oil based adjuvants will likely result in reduced performance.

APPLICATION
Ground application: Apply with flat fan nozzles in a spray volume of 80–150L of water per hectare using standard boom spraying equipment. Application as a MEDIUM spray quality (defined by ASAE S572 Standard) using air induction nozzles is recommended. In advanced or dense weed infestations and/or dense crop canopies, increase the water volume to ensure adequate coverage.

RE-ENTRY PERIOD
Do not allow entry into treated areas until spray has dried. If prior entry is necessary wear cotton overalls buttoned

to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

COMPATIBILITY

FREQUENCY® Herbicide is physically compatible with Axial®*, Bromoxynil (including Bromicide®* 200 Selective Herbicide, Bronco®* 200 Herbicide, Genfarm Bromo 200 Herbicide, Titan Bromoxynil 200 Selective Herbicide), Flight®* EC, MCPA L.V.E (including Polo®* 570 LVE Herbicide, Nufarm LVE Agritone®* Selective Herbicide, Nufarm Agritone®* 750 Selective Herbicide, Genfarm MCPA LV 570 Herbicide, Titan LVE MCPA 570 Herbicide, Adama MCPA LVE 570 EC Herbicide), Metsulfuron (Ally®*, Associate®*), Jaguar®*, Paragon®* Xtra, Sencor®* 480 SC, Tigrex®* and Topik® 240 EC.

FREQUENCY® Herbicide is physically compatible with Easy N®* liquid fertiliser. Consult BASF staff for full compatibility details when utilising Easy N® in mixes with herbicide combinations. The use of Easy N® with FREQUENCY® Herbicide may result in transient crop burn.

Product Use	Herbicide Mix Partner Product	Comments
FREQUENCY® Herbicide + Bromoxynil 200g/L bromoxynil as N-octanoyl ester + Hasten Adjuvant or + MCPA (L.V.E) - 570g/L MCPA as 2-ethylhexyl ester + Hasten Adjuvant	Metsulfuron - Metsulfuron-methyl (600g/kg)	Observe use restrictions and plant back comments on mix partner labels. Mixtures with picolinofen or diflufenican may cause increased foliar burn however crop yield will not be adversely affected.
	Tigrex®* 250g/L MCPA as 2-ethylhexyl ester + 25g/L diflufenican	
	Jaguar®* 25g/L diflufenican + 250g/L Bromoxynil present as the octanoate	
	Paragon®* Xtra 210g/L Bromoxynil present as the n-octanoyl ester + 350g/L MCPA present as the ethyl hexyl ester + 35g/L Picolinafen	
	Flight®* EC 210g/L Bromoxynil present as the n-octanoyl ester + 350g/L MCPA present as the ethyl hexyl ester + 35g/L Picolinafen	
	Sencor®* 480 480g/L metribuzin	
	Topik®* 240 240g/L clodinafop-propargyl + 60g/L cloquintocet	
	Axial®* 100g/L pinoxaden + 25g/L cloquintocet	
FREQUENCY® Herbicide + Bromoxynil 200g/L bromoxynil as N-octanoyl ester + Hasten Adjuvant or + MCPA (L.V.E) - 570g/L MCPA as 2-ethylhexyl ester + Hasten Adjuvant	Liquid urea ammonium nitrate fertilizer (UAN)	Increased crop leaf burning may occur however yields will not be negatively impacted

As water quality can influence compatibility, it is recommended that mixtures should be bottle-tested in the water

intended for spraying, prior to mixing commercial quantities.

CROP SAFETY

DO NOT apply to crops undersown with legumes and other broadleaf fodder.
Following application, some transient bleaching (white spotting and/or mottling) of cereal foliage may occur especially with high light activity on young crops. This bleaching is confined to leaves present at application. The development of the crop and subsequent new growth is unaffected in crops growing free of stress. Symptoms will be more pronounced and persistent in crops that are growing under stress, particularly under frost conditions (see Restraints).

SPRAYER CLEANUP

Following use, the sprayer should be cleaned before spraying sensitive broadleaf crops. Empty the tank completely and drain the whole system. Quarter fill the tank with clean water directing stream onto inside of tank. Circulate through the pump, the hoses and nozzles then drain. Repeat if necessary. Finally remove and clean all filters (tank, in-line and nozzle) separately. This will provide an effective cleaning technique for FREQUENCY® Herbicide. A boom cleaner may be used as part of the procedure.

HERBICIDE RESISTANCE WARNING

GROUP	H	HERBICIDE

FREQUENCY® Herbicide is a member of the benzoylpyrazole group of herbicides and acts by inhibiting 4-hydroxyphynlpyruvate dioxygenase (4-HPPD). For weed resistance management FREQUENCY® Herbicide is a Group H herbicide. Some naturally occurring weed biotypes resistant to this product and other Group H 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 H herbicides. Since the occurrence of resistant weeds is difficult to detect prior to use, BASF Australia Limited accepts no liability for any losses that may result from the failure of this product to control resistant weeds.

Resistance Management

Management of weed resistance to Group H herbicides is important to maintain this critical mode of action for broadleaf weed control and particularly for wild radish control. Where possible, FREQUENCY® Herbicide should be used as a part of an integrated weed management program which includes herbicides from other modes of action and non-chemical methods. CropLife resistance management strategies are available from BASF sales representatives and from CropLife at www.croplife.com.au.

CROP PLANT BACK & ROTATION RECOMMENDATIONS

FREQUENCY® Herbicide does not provide long-term residual activity; however, certain crops show sensitivity to soil residues. Refer to the following table for application-to-sow intervals applicable to the maximum label rate.

Plant Back Interval	6 weeks after FREQUENCY® Herbicide application	4 months after FREQUENCY® Herbicide application	9 months after FREQUENCY® Herbicide application

Crop	Wheat Barley Maize	Canola Chickpeas Faba beans Field peas Lentils Lupins Mungbeans Safflower Sorghum Sunflower Cotton	All other crops

Check the label of any product mixed with FREQUENCY® Herbicide, to determine any plant back periods or restrictions on use.

PROTECTION OF WILDLIFE, FISH, CRUSTACEA AND ENVIRONMENT

Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

STORAGE

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

DISPOSAL

5L, 10L, 15L, 20L

Triple-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.

110L

Empty container by pumping through the drybreak Micro Matic connection system. DO NOT attempt to unscrew the Micro Matic valve or breach the locked filing point. DO NOT contaminate the container with water or other foreign material. Ensure that the Micro Matic coupler, pump, meter and hoses are disconnected, triple rinsed with clean water and drained after each use. When empty, or contents no longer required, return the container to the point of purchase. DO NOT dispose of undiluted chemicals on-site.

SAFETY DIRECTIONS

Harmful if inhaled. Will irritate the eyes and skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. Do not inhale vapour. If product on skin immediately wash area with soap and water. If product in eyes, wash it out immediately with water. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow length chemical resistant gloves and face shield or goggles. If applying by boomspray equipment (open cab) wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). Wash hands after use. After each day use, wash gloves, face shield or goggles and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre. *Phone Australia 131126; New Zealand 0800 764 766.* If swallowed, do NOT induce vomiting.

SAFETY DATA SHEET
Additional information is listed in the Safety Data Sheet available from your supplier.

CONDITIONS OF SALE
All conditions and warranties rights and remedies implied by law or arising in contract or tort whether due to the negligence of BASF Australia Ltd or otherwise are hereby expressly excluded so far as the same may legally be done provided however that any rights of the Buyer pursuant to non- excludable conditions or warranties of the Competition and Consumer Act 2010 or any relevant legislation of any State are expressly preserved but the liability of BASF Australia Ltd or any intermediate Seller pursuant thereto shall be limited if so permitted by the said legislation to the replacement of the goods sold or the supply of equivalent goods and all liability for indirect or consequential loss or damage of whatsoever nature is expressly excluded. This product must be used or applied strictly in accordance with the instructions appearing hereon. This product is solely sold for use in Australia and must not be exported without the prior written consent of BASF Australia Ltd.

APVMA Approval No: 86267/115160
Batch No:
Date of Manufacture:

BASF
We create chemistry

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ABBREVIATIONS

acs	active constituents
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
DAT	Days After Treatment
DT_{50}	Time taken for 50 per cent of the concentration to dissipate
DFOP	Double first-order in parallel
EC_{50}	concentration at which 50 per cent of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50 per cent of the test population is impacted
ESI	Export Slaughter Interval
EUP	End Use Product
g	gram
GAP	Good Agricultural Practice
GLP	Good Laboratory Practice
ha	hectare
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
K_d	adsorption constant
K_f	Freundlich absorption coefficient
$K_{f,oc}$	Freundlich organic carbon absorption coefficient
kg	kilogram
K_{OC}	organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50 per cent of the test population of organisms

LD_{50}	dosage of chemical that kills 50 per cent of the test population of organisms
LOD	Limit of Detection–level at which residues can be detected
Log K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}
LOQ	Limit of Quantitation–level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
NOEC/NOEL	No Observable Effect Concentration Level
NOEL	No observable effect concentration
NOAEL	No Observed Adverse Effect Level
pF2	reference condition for soil moisture, field capacity 10kPa
PPE	Personal Protective Equipment
SC	Suspension Concentrate
SE	Suspo-emulsion
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGAI	technical grade active ingredient
TRR	total radioactive residues (TRR
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
Metabolism	The chemical processes that maintain living organisms
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

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