Australian Government

Australian Pesticides and Veterinary Medicines Authority

# Public Release Summary

on the evaluation of the new active metcamifen in the product EPIVIO C Sorghum Seed Safener

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This publication is available from the APVMA website.

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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 Public Release Summary 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 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the approval of the new active metcamifen and registration of the product EPIVIO C Sorghum Seed Safener 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 2 June 2020 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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Sydney NSW 2001

**Phone:** +61 2 6770 2300

**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 EPIVIO C Sorghum Seed Safener, and approval of the new active constituent, metcamifen.

## 1.1 Applicant

Syngenta Australia Pty Ltd.

## 1.2 Purpose of application

Syngenta Australia Pty Ltd has applied to the APVMA for approval of the new active constituent, metcamifen and registration of the new product EPIVIO C Sorghum Seed Safener, containing 400 g/L metcamifen, formulated as a suspension concentrate for seed treatment.

## 1.3 Proposed claims and use pattern

The proposed product EPIVIO C Sorghum Seed Safener is intended for use as a seed treatment for protection from the phytotoxic effects of S-metolachlor.

## 1.4 Mode of action

Metcamifen stimulates production of glutathione-S-transferase (GST) enzymes. Glutathione S-transferases, previously known as ligandins, comprise a family of eukaryotic and prokaryotic phase II metabolic isozymes best known for their ability to catalyse the conjugation of the reduced form of glutathione to xenobiotic substrates for the purpose of detoxification.

The production of GSTs in the germinating sorghum seed therefore confers a level of tolerance to the phytotoxic effects of S-metolachlor and related compounds present in the soil at the time of crop germination.

## 1.5 Overseas registrations

The product is currently registered in China as EPIVIO C for seed treatment of corn seed to safen against post-emergence herbicide applications. Metcamifen is also registered in the USA as a formulation inert, with intended use as safener following foliar application of herbicides.

# 2 CHEMISTRY AND MANUFACTURE

## 2.1 Active constituent

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

Metcamifen is an odourless white powder. It is practically insoluble in water under acidic conditions (32 mg/L at 25°C and pH 5.5), becoming more soluble under alkaline conditions due to ionisation (79 g/L at 25°C and pH 8.7). It has low solubility in methanol, dichloromethane, ethyl acetate and n-hexane. It has moderate solubility in acetone (28 g/L) and toluene (22 g/L). Metcamifen is not volatile at ambient temperatures. Neither the purified active ingredient nor the technical grade active ingredient are surface-active. There are no safety properties (eg flammability, explosive, and/or oxidizing) of concern regarding metcamifen. Metcamifen is expected to be stable for at least two years storage under normal conditions.

**Table 1: Nomenclature and structural formula of the active constituent metcamifen**

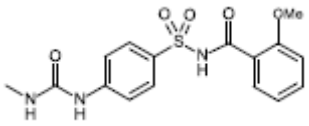
| | |
|---|---|
| **Common name (ISO):** | Metcamifen |
| **IUPAC name:** | 2-Methoxy-*N*-{4-[(methylcarbamoyl)amino](benzene-1-sulfonyl)}benzamide |
| **CAS registry number:** | 129531-12-0 |
| **Molecular formula:** | $C_{16}H_{17}N_3O_5S$ |
| **Molecular weight:** | 363.4 |
| **Structural formula:** |  |

Table 2: Key physicochemical properties of the active constituent metcamifen

| | |
|---|---|
| **Physical form:** | Solid |
| **Colour:** | White powder |
| **Odour:** | Odourless |
| **Melting point:** | 209.8°C ± 0.27% |
| **Boiling point:** | The test substance decomposes at 269°C |
| **Relative density** | 1.43 g/mL at 20°C |
| **Stability:** | At ambient temperature, metcamifen was shown to be stable for at least 1 year. At elevated temperatures, no changes in the active were observed after 2 weeks storage at 54ºC. No adverse reactions with metals or metal ions (iron and aluminium, and aluminium acetate and iron acetate) were observed following storage at 20ºC and 40ºC for 7 days and 14 days, respectively. Technical metcamifen is therefore expected to be stable on storage for at least 2 years under normal conditions. |
| **Safety properties:** | Not considered flammable. Not explosive. Not auto-flammable. Except photo-degradation in water, the metcamifen technical does not show any chemical incompatibility with oxidising and reducing agents and is essentially non-hazardous. |
| **Solubility in water:** | 32 mg/mL (pH 5.5)<br>45 mg/mL (pH 5.1)<br>2 g/L (pH 6.8)<br>79 g/L (pH 8.7) at 25ºC |
| **Organic solvent solubility:** | Acetone 28 g/L<br>Ethyl acetate 4.1 g/L<br>Toluene 22 g/L<br>Dichloromethane 5.5 g/L<br>Methanol 9.5 g/L<br>Octanol 1.1 g/L<br>Hexane < 1 mg/L |
| **Dissociation constant ($PK_a$):** | pKa = 4.55 at 25ºC |
| **PH:** | pH 4.6 at a 1% dilution in pure water at 25ºC |
| **Octanol/water partition coefficient (Log $K_{ow}$/$K_{OW}$):** | log $K_{ow}$ = 1.4, pH 5.1<br>log $K_{ow}$ = -0.3, pH 7.0<br>log $K_{ow}$ = -2.0, pH 9.0 at 25ºC |
| **Vapour pressure:** | <6.3 × $10^{-6}$ Pa at 20ºC and 25ºC |
| **Henry's law constant:** | < 1.14 × $10^{-6}$ Pa $m^3$/mol |

| | |
|---|---|
| UV/VIS absorption spectra: | $\lambda_{max}$265 nm, neutral solution<br>$\lambda_{max}$272 nm, acetic solution<br>$\lambda_{max}$261 nm, basic solution |

## 2.2 Formulated product

The product EPIVIO C Sorghum Seed Safener will be manufactured overseas. Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

EPIVIO C Sorghum Seed Safener will be available in 500 mL to 100 L HDPE (high density polyethylene) containers.

**Table 3: Key aspects of the formulation of the product EPIVIO C Sorghum Seed Safener**

| | |
|---|---|
| Distinguishing name: | EPIVIO C Sorghum Seed Safener |
| Formulation type: | Suspension concentrate for seed treatment (FS) |
| Active constituent concentration: | 400 g/L metcamifen |

**Table 4: Physicochemical properties of the product EPIVIO C Sorghum Seed Safener**

| | |
|---|---|
| Physical form: | Off-white liquid |
| PH: | 5.3 (1% aqueous dilution) |
| Density: | 1.177 g/cm$^3$ at 20ºC |
| Kinematic viscosity: | 213 mPa$^{-s}$ at 20ºC and 196 mPa$^{-s}$ at 40ºC |
| Pourability: | Pour residue = 2.9%; rinsed residue = 0.1% |
| Persistent foaming: | 0 mL foam (50% and 20% dilution) after 1 minute |
| Suspensibility: | 99% (50% dilution) and 94% (20% dilution) |
| Corrosion of metal: | No corrosion on stainless steel |
| Safety properties: | No flash point below 100°C. Auto-ignition temperature is 520°C. No exothermic decomposition. Not classified as a flammable liquid or an explosive and/or as an oxidising substance. |
| Storage stability: | There was sufficient data to conclude that the product is expected to remain within specifications for at least 2 years when stored under normal conditions |

## 2.3 Recommendations

The APVMA has evaluated the chemistry of the active constituent metcamifen and associated product EPIVIO C Sorghum Seed Safener, including the manufacturing process, quality control procedures, identification, physicochemical properties, 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 EPIVIO C Sorghum Seed Safener, and approval of the active constituent metcamifen, are supported from a chemistry perspective.

# 3 TOXICOLOGICAL ASSESSMENT

## 3.1 Evaluation of toxicology

### Chemical class

Metcamifen is an acyl sulfonamide seed safener.

### Pharmacokinetics

Following administration to mice and rats, up to about 85 per cent of an oral dose of metcamifen was absorbed rapidly from the gastro-intestinal tract and distributed mainly to the liver, kidney, small intestine, urinary bladder, urine and lung. Absorption was saturated at higher doses, with less than proportional increases in the concentration of metcamifen in the blood and plasma. Male rats mainly metabolised metcamifen by O-demethylation, but this pathway was markedly less active in females. Rats of both sexes produced smaller amounts of at least five other metabolites by N-demethylation, sulphonamide group cleavage, hydroxylation, conjugation with glucuronic acid and formation of hydroxy-metcamifen sulphate.

Metcamifen and its metabolites were eliminated readily, with most of an oral dose depleted from the gastro-intestinal tract, circulation and tissues by 48 hours after administration. Excretion was essentially complete within one week. Rats excreted up to two-thirds of a low dose of metcamifen via the urine, with the remainder appearing in the faeces. At high doses, however, up to 85 per cent of administered metcamifen was eliminated via the faeces, reflecting the reduced extent of gastro-intestinal absorption. No more than about three per cent of a dose was eliminated in the bile. When radiolabelled metcamifen was given to goats for a week in their feed, up to 45 per cent and 50 per cent of administered radioactivity was voided in the urine and faeces, respectively, and a small fraction was secreted in milk.

### Acute toxicity (active constituent)

Metcamifen was of very low acute toxicity in rats. No mortality or clinical signs occurred and no abnormal pathological findings were made at the highest administered oral and dermal doses of 5000 mg/kg bw. When metcamifen dust was administered by inhalation for four hours at 5060 mg/m$^3$, laboured respiration was observed but there were no deaths or pathological abnormalities. In rabbits, metcamifen powder was not a skin irritant but caused slight eye irritation. Metcamifen did not cause skin sensitisation in a local lymph node assay in mice.

### Acute toxicity (product)

EPIVIO C Sorghum Seed Safener was of low acute toxicity with oral and dermal LD50s of >2000 mg/kg bw and an inhalational LC50 of >3490 mg/m$^3$ in rats. The product was not irritating or sensitising to the skin but was a slight eye irritant in rabbits.

## Repeat-dose toxicity

Repeat dose studies by oral administration to mice, rats and dogs showed relatively few adverse effects, predominantly involving the blood, liver and testis in male rats and the ovary in female rats. In 28-day and/or 13 week dietary toxicity studies, male (but not female) rats treated with metcamifen at 16,000 ppm (1300–1600 mg/kg bw/d) displayed slight to moderate increases in clotting times and blood fibrinogen levels, as well as clinical chemistry changes (increased urea nitrogen, cholesterol concentrations and ALT activity). These were not correlated with histopathological findings but may have arisen from metabolic disturbances within liver cells, possibly associated with the gender-related differences in the routes via which metcamifen is metabolised. Some male rats that received metcamifen at 16,000 ppm during the 13 week study were affected by degeneration of the testicular seminiferous epithelium and had reduced numbers of sperm in the epididymides. The effects were not observed at or below 4800 ppm (355 mg/kg bw/d), or during the equivalent studies with mice and dogs at the highest administered doses of 1003 and 100 mg/kg bw/d, respectively.

When metcamifen powder was applied to the skin at 1000 mg/kg bw/d for 28 days, rats displayed transient depression in food consumption, bodyweight gain and/or bodyweight. However, there was no mortality, skin irritation or evidence of systemic toxicity, and so the NOAEL was set at 1000 mg/kg bw/d.

## Chronic toxicity and carcinogenicity

In an 80 week dietary study in mice, transient effects on bodyweight gain were seen, which were not considered to be adverse. The NOAEL was therefore established at 750 ppm (90 and 95 mg/kg bw/d in males and females, respectively), the highest dose tested. After 104 weeks of dietary treatment with metcamifen at 2400 ppm (178 mg/kg bw/d), female rats displayed enlargement of and increased synthesis of red blood cells in the spleen, and increased incidences of ovarian cysts and hyperplasia (but not tumours). Based on these findings, the NOAEL in females was 600 ppm (45 mg/kg bw/d).

Metcamifen did not display carcinogenic activity in mice treated for 80 weeks by dietary admixture at up to and including 750 ppm. There was also no treatment-related increase in cancer during a 104 week study in rats at dietary levels of up to 4000 ppm in males (230 mg/kg bw/d) and 2400 ppm in females (178 mg/kg bw/d).

## Reproductive and developmental toxicity

In a two-generation dietary reproduction toxicity study in rats, there were no effects on body weights, food intake, reproductive performance, mating behaviour, conception or pup survival and development in either the parental or F1 generations. The overall study NOAEL was 191 mg/kg bw/d for reproductive, parental and offspring toxicity.

In a developmental study in rats, there were no effects on embryo-foetal survival, growth or sex ratio and no treatment-related increases in external, visceral or skeletal abnormalities or variations in the foetuses. The NOAEL for maternal toxicity and foetal effects was 2000 ppm (180 mg/kg bw/d).

In rabbits, there was no evidence of maternal toxicity at up to and including 150 mg/kg bw/day. There were also no treatment-related effects on embryo-foetal survival, or increases in external or visceral abnormalities

or variations in the foetuses. An increase in minor abnormalities and variations affecting the skeleton and cartilage, most of which involved the spinal vertebrae, ribs, sternum, maxilla, tibia and femur was seen from 65 mg/kg bw/day. These variations are characterised as divergences beyond the normal structural range which may not adversely affect survival or health, and were considered likely to be related to delayed development of the bones and/or cartilage. Although a number of these variations were seen at rates lying within control values, and may be considered to arise by chance, other variations were above this level and may be related to treatment. The possibility of these variations being related to treatment could not be ruled out, and on this basis, the NOAEL for embryo-foetal toxicity was considered to be 30 mg/kg bw/d and for maternotoxicity was 150 mg/kg bw/d. However, given that these effects were minor variations likely related to overall delays of development in the offspring of treated rabbits, the overall conclusion was that metcamifen will pose negligible risk of developmental toxicity in humans.

### Genotoxicity

Metcamifen was not genotoxic in a range of in vivo and in vitro tests.

### Neurotoxicity/immunotoxicity

An acute neurotoxicity study was performed with metcamifen in rats. Transient fur ruffling, hypothermia, decreased locomotor activity and depressed food consumption occurred in females at 2000 mg/kg bw but were not observed after the day of dosing. There were no treatment-related pathological abnormalities in the peripheral or central nervous systems, so NOAELs of 1000 and 2000 mg/kg bw/d were respectively assigned for general toxicity and neurotoxicity.

### Toxicity of metabolites and/or impurities

Acute toxicity and genotoxicity studies were performed with CGA214513, which is an impurity of technical grade metcamifen, a metabolite of metcamifen in rats, chickens and goats; a tissue residue in chickens (and eggs) and goats (and milk); and also a metabolite or degradation product in plants, soil and water.

CGA214513 was of low acute toxicity in rats. No mortality or clinical signs occurred and no abnormal pathological findings were made at the highest administered oral and dermal doses of 2000 mg/kg bw. When CGA214513 was administered as a dust by inhalation at 5020 mg/m$^3$, laboured respiration was observed but there were no deaths or pathological abnormalities. The test compound yielded negative findings in irritation and corrosivity assays using reconstructed human epidermis; was slightly irritating to the rabbit eye; and did not cause dermal sensitisation in mice.

CGA214513 did not exhibit mutagenic activity in the presence or absence of metabolic activation in a reverse mutation assay in bacteria at concentrations of up to 5000 µg/plate or in cultured mouse lymphoma cells at up to 2300 µg/mL. The test compound was also negative for structural damage to chromosomes in isolated human lymphocytes at up to 2000 µg/mL with or without metabolic activation.

## 3.2 Health-based guidance values and poisons scheduling

### Poisons Standard

The Scheduling Delegate has determined that metcamifen does not meet the factors for inclusion in the Schedules of the Poisons Standard. Metcamifen has been listed in Appendix B due to low toxicity. The product, EPIVIO C Sorghum Seed Safener does not contain any ingredients included in a Schedule of the Poisons Standard, and is therefore unscheduled.

### Health-based guidance values

#### *Acceptable Daily Intake*

An Acceptable Daily Intake (ADI) of 0.30 mg/kg bw/d was established for metcamifen based on the NOAEL of 30 mg/kg bw/d for an increased incidence of skeletal and cartilage variants of the vertebrae and ribs in a study of developmental toxicity in rabbits, and an uncertainty factor of 100.

#### *Acute Reference Dose*

An Acute Reference Dose (ARfD) of 0.30 mg/kg bw was established for women of child-bearing age based on a NOEL of 30 mg/kg bw/d for an increased incidence of skeletal and cartilage variants of the vertebrae and ribs, which might be attributable to a single exposure to metcamifen at $\geq$65 mg/kg bw/d in a study of developmental toxicity in rabbits, with an uncertainty factor of 100.

Based on its acute toxicity profile it was concluded that the establishment of an ARfD for the general population was not necessary for metcamifen on the basis of its low acute toxicity, the lack of evidence for any acute neurotoxicity and the absence of any other toxicologically relevant effect that might be attributable to a single dose.

## 3.3 Recommendations

There are no objections on human health grounds to the approval of metcamifen, or to registration of the product EPIVIO C Sorghum Seed Safener containing metcamifen at 400 g/L.

After consideration of the toxicological profile and likely human exposure associated with the use of EPIVIO Sorghum Seed Safener, and its active constituent, metcamifen, the APVMA concludes that the human health risks are acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act 1994* (as amended), for all proposed application methods in accord with the label directions for use; of workers re-handling or planting treated seed; or of bystanders and the public.

# 4 RESIDUES ASSESSMENT

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

## 4.1 Metabolism

The metabolism and distribution of metcamifen (CGA246783) has been investigated in maize, rice, rotational crops, hen and goat. In all studies the active substance was radiolabelled in the aniline ring and in the benzoyl ring in separate experiments.

### Plants

Following seed treatment with paddy rice (121 to 124 g ai/100 kg seeds), uptake and translocation of parent metcamifen and its metabolites into grain was low (≤0.034 mg eq./kg). No individual identified component in grain commodities accounted for >0.001 mg eq./kg and there was evidence of natural incorporation. Therefore, no significant residues in food items following seed treatment with metcamifen are expected. Higher total residues were observed in animal feed commodities with the largest residues observed in hay (0.148 mg eq./kg). Metabolism was extensive with forage, the only commodity where the residue level of parent exceeded 0.01 mg eq./kg (12–14 per cent TRR in forage [0.008 to 0.015 mg/kg]). The principal identified components in feed commodities were the aniline specific metabolite CGA214513 and a lactate conjugated form of CGA214513, and CSDK468200 (unknown metabolite), accounting for maximums of 11 per cent (0.016 mg eq./kg) and 31 per cent (0.040 mg eq./kg) respectively.

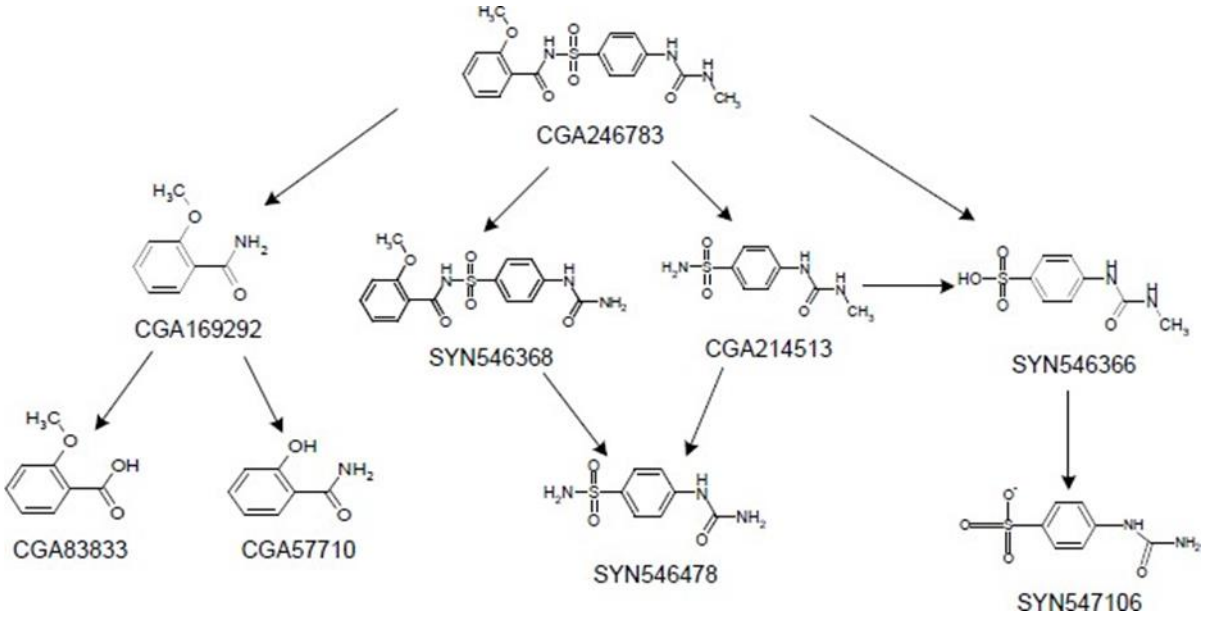
Following a single application to soil at 200g a.i./ha, residues in maize food commodities (cobs and grains) were low (< 0.01 mg eq./kg). Metabolism in maize was extensive and parent was only detected in forage at 6.4 per cent TRR (0.001 mg eq./kg). The principal identified metabolite in forage and stover was CGA214513 which was observed in both its free and conjugated form and accounted for a maximum of 32 per cent TRR (0.005 mg eq./kg). Also identified at lower levels were SYN546478 (aniline specific metabolite) and SYN546368 (which retained both the aniline and benzoyl rings of metcamifen) at ≤ 13 per cent TRR. Absolute residues of each identified metabolite did not exceed 0.006 mg eq./kg.

Following foliar and soil application in maize both at 200g a.i./ha, residues were highest in feed commodities (forage and stover) with the largest residues observed in stover following pre- and post-emergence applications. Residues in cobs and grains were again <0.01 mg eq./kg. Metabolism was extensive and parent was not detected in forage or stover. The principal identified metabolite in forage and stover was SYN546366 occurring via cleavage between the aniline and benzoyl ring systems of metcamifen. SYN546366 was observed in its free form only and accounted for a maximum of 31.4 per cent TRR and 0.035 mg eq./kg. Also identified were corresponding metabolites which retained only the benzoyl ring of parent metcamifen; CGA057710 and CGA169292 accounting for a maximum of 22 per cent TRR (0.022 mg eq./kg) and 11 per cent TRR (0.011 mg eq./kg) respectively.

In a confined rotational study aniline- and benzoyl-labelled $^{14}$C-metcamifen (EC formulations) were applied to containers of soil at a rate of 95.2 and 97.1 g a.i./ha respectively which is approximately 25 to 40× the

proposed application rate based on 2.5 to 4 kg seed /ha (2.5 to 4 g a.i./ha). TRRs were ≤ 0.037 mg eq./kg in representative rotational crops sown 30, 120, and 270 days after application (DAA) of the test substance to a sandy loam soil at a nominal rate of 100 g ai/ha. TRR levels resulting from both the aniline and the benzoyl label treatments were observed to be <0.01 mg eq./kg in lettuce, turnip foliage, turnip tubers and wheat forage from the 30, 120 and 270 DAA rotational intervals. TRR levels were observed to decrease progressively with increasing rotational interval (all residues ≤0.002 mg eq./kg in these commodities by the 270 DAA rotational interval harvest). TRR levels in wheat grain, hay and straw were ≥0.01 mg eq./kg in some of the 30 DAA interval samples with a maximum of 0.037 mg eq./kg in straw (aniline ring). TRR levels >0.01 mg eq./kg in the 120 DAA interval samples were found only in straw, being 0.016 mg eq./kg (aniline ring) and 0.012 mg eq./kg (benzoyl ring). No residues were found >0.01 mg eq./kg in any wheat samples by the 270 DAA rotation interval. The principle biotransformation observed was cleavage of the sulphonamide linkage to yield CGA214513. Overall uptake into rotated crops was low with no single component exceeding 0.006 mg eq./kg.

### The biotransformation pathway for metcamifen in maize




## Animals

In the hen and goat studies, the majority (>76 per cent) of the dosed radioactivity was excreted. Parent metcamifen was detected in all hen tissue and egg samples at ≤0.018 mg/kg. In the goat study, metcamifen was detected only in milk (2.3 per cent TRR, 0.006 mg/kg) and kidney (6.0 per cent TRR, 0.016 mg/kg) from the aniline label experiment and in kidney (18 per cent TRR, 0.022 mg/kg) from the benzoyl label experiment.

In hens, the only identified metabolites in tissues and egg arose via cleavage of the sulphonamide linkage and were the sulphonamide metabolite, CGA214513 (46 to 109 per cent TRR, 0.013 to 0.057 mg eq./kg) detected in liver, egg yolk and white, muscle and skin and fat and the methoxy benzoic acid metabolite, CGA83833 (<50 per cent TRR, ≤0.006 mg eq./kg) which was detected in liver and egg yolk and white only.

In goats, the major residue in tissues and milk for the aniline label experiment was CGA214513 (71 to 88 per cent TRR, 0.027 to 0.191 mg eq./kg). Unchanged metcamifen and SYN546478 accounted for <6.0 per cent TRR. The major residues in tissues and milk for the benzoyl label experiment were 2[(2- methyoxyphenyl) formamido] acetic acid (19 to 75 per cent TRR, 0.004 to 0.024 mg eq./kg) and CGA83833 (28 to 60 per cent TRR, 0.005 to 0.075 mg eq./kg). Unchanged metcamifen, CGA169292 and CGA277776 accounted for ≤17.5 per cent TRR.

## 4.2 Analytical methods and storage stability

In the submitted Australian sorghum residues trials metcamifen residues were twice extracted from each blended homogenous sample with acetonitrile/water mixtures. The extracts were combined and filtered. An aliquot of the sample extract was evaporated to near dryness, and then reconstituted in methanol/water. Metcamifen residues were determined by liquid chromatography coupled with a tandem mass spectrometer (LC-MS/MS) using external matrix standards. The limit of quantitation (LOQ) and the limit of detection (LOD) of the method were determined as 0.01 mg/kg and 0.003 mg/kg respectively. Validation results were within acceptable limits.

The multi-residue QuEChERS method was used for the determination of residues of metcamifen and CGA214513 in animal matrices (whole milk, bovine muscle, bovine liver, whole eggs, and bovine fat). Bovine liver, whole eggs, and bovine fat recovery samples were initially hydrated with ultra-pure reagent water with the aid of a grinder. All animal tissues samples were extracted with acetonitrile using a grinder. Partitioning was then aided with buffered salts (magnesium sulphate, sodium chloride and sodium citrate dibasic sesquihydrate) and extraction repeated using a grinder. Following extraction, samples were centrifuged and the supernatant removed. Whole milk samples were further processed via dispersive SPE clean-up for analysis of CGA214513 only. All samples were diluted into the calibration standard range with acetonitrile/ultra-pure water. All samples and standards were analysed using LC-MS/MS. The limit of quantitation was 0.01 mg/kg for each analyte in each matrix.

Metcamifen and its metabolites SYN546366 and CGA214513 were stable in frozen storage (–25 to –10°C) for up to least 18 months in corn grain, corn meal, lettuce, canola oil, orange oil, soybean, flaxseed meal, orange, orange juice, and carrot, with the exception of SYN546366 in orange oil, which was shown to be stable up to 12 months.

In the residue trials submitted, all samples were maintained under freezer conditions, (ie –18°C) prior to analysis and tested within <10 months. This is acceptable for the purposes of the current application.

## 4.3 Residue definition

### Plants

As parent metcamifen is the major component of the residue in some plant commodities, it should be included in the residue definition. CGA214513 which is the metabolite which is most commonly observed in feed commodities, is considered to be of low toxicological significance. Noting that quantifiable residues of neither parent nor a metabolite are expected in sorghum grain, forage or fodder, a residue definition of

parent metcamifen only, is considered appropriate for both enforcement and risk assessment of metcamifen residues for commodities of plant origin for the proposed use on sorghum.

### Animals

As parent metcamifen was detected in all hen tissue and egg samples and in goat milk and kidney, it should be part of the residue definition. CGA214513 (4-(3-methyl-ureido)-benzensulfonamide was observed to be the major component of the residues in most commodities of both hens and goats, so should also be part of the residue definition. A residue definition of the sum of metcamifen and 4-(3-methyl-ureido)-benzensulfonamide, expressed as metcamifen, is considered appropriate for enforcement and risk assessment of metcamifen residues for commodities of animal origin.

## 4.4 Residues in food and animal feeds

The proposed Good Agricultural Practice (GAP) for EPIVIO C Sorghum Seed Safener for use on sorghum as a seed treatment, is for a maximum of one application of metcamifen at 100 g a.i./100 kg of seed. The proposed harvest WHP is 'Not required when used as directed' with a six week grazing WHP.

In five trials conducted in Australia, residues in sorghum seed at commercial harvest, 89–142 days after one seed treatment application at 100 and 200 g a.i./100 kg of seed (1× and 2× the proposed application rate) were: <LOD (ie <0.003) mg/kg (n=5).

It is considered appropriate to establish an MRL at the LOQ of *0.01 mg/kg for GC 0651 sorghum, for the proposed uses of metcamifen on sorghum.

Residues in sorghum stubble at commercial harvest, 89 to 142 days after one seed treatment application at 100 or 200 g a.i./100 kg of seed were: <LOD (5) mg/kg on a dry weight basis.

It is considered appropriate to establish an MRL at *0.01 mg/kg for AS 0651 sorghum straw and fodder (dry), for the proposed uses of metcamifen on sorghum.

Residues in sorghum forage at the proposed six week grazing WHP after one seed treatment application at 100 g a.i./100 kg of seed were, in rank order: <LOD (5) and <0.01 mg/kg (<LOD (5) and 0.004 mg/kg) on a fresh weight basis.

It is considered appropriate to establish an MRL at *0.01 mg/kg for AF 0651 sorghum forage (green) [fresh weight], for the proposed uses of metcamifen on sorghum.

## 4.5 Crop rotation

Sorghum is a rotational crop in Australia. The confined rotational study which was conducted at an exaggerated application rate, indicates that no quantifiable residues of either parent compound or any metabolites are expected after application at the proposed rate of 100 g a.i./100 kg seed.

In the submitted Australian field trials, no quantifiable residues of metcamifen were observed in any sample (including forage taken at six weeks after application) after application at 1 and 2× the proposed application rate.

It is considered unlikely that any following crops could take up residues at a quantifiable level and no plant-back interval is therefore considered to be necessary from a residues and trade perspective, nor are MRLs for following crops.

## 4.6 Residues in animal commodities

Sorghum grain, forage and fodder are considered to be significant animal feeds. Animal transfer studies for metcamifen have not been provided however were not required as quantifiable residues are not expected in sorghum forage, sorghum straw and fodder and sorghum grain arising from the proposed use.

The goat metabolism study (application at 12.9 to 13.0 ppm in the feed, 1290 to 1300× assuming residues at 0.01 mg/kg in animal feeds) in which the highest amount of any analyte was 0.191 mg/kg of CGA214513 in kidney, suggests that no detectable residues of parent or any metabolite will be observed in livestock commodities following application at the proposed rate.

The hen metabolism study (application at 14.9 to 23.9 ppm in the feed, 1490 to 2390× assuming residues at 0.01 mg/kg in animal feeds) in which the highest amount of any analyte was 0.018 mg/kg of parent metcamifen in skin and fat, suggests that no detectable residues of parent or any metabolite will be observed in poultry commodities following application at the proposed rate.

Noting that the proposed residue definition for animal commodities is the sum of metcamifen and CGA214513, expressed as metcamifen, the MRLs will be set for mammalian and poultry commodities at the combined LOQs for metcamifen and CGA214513 (0.01 mg/kg for both). Noting that the molecular weight of CGA214513 is 229.05, the LOQ for CGA214513 in parent equivalents is 0.01 × 363.4/229.05 mg/kg = 0.016 mg/kg, as parent equivalents. The combined LOQ is therefore 0.026 mg/kg (rounded to 0.03 mg/kg).

No data was provided to demonstrate the residue potential of direct feeding of treated seed to livestock as that was not the intention of the use. In the absence of relevant data, the following restriction is supported:

Treated seed must be clearly labelled ‘EPIVIO C treated for Dual Gold Herbicide and Primextra Gold Herbicide pre-emergent weed control’ and carry the warning. ‘DO NOT feed to animals’.

### Bioaccumulation potential

The $K_{ow}$ logP for metcamifen is 1.4 at pH 5.1 and 25°C, –0.30 at pH 7.0 and 25°C and –2.0 at pH 7.0 and 25°C indicating a low potential for fat solubility and bioaccumulation in fat. The mammalian and poultry meat MRLs will not be established ‘in the fat’.

## 4.7 Dietary risk assessment

The chronic dietary exposure to metcamifen 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 metcamifen is equivalent to <1 per cent of the ADI.

It is concluded that the chronic dietary exposure to metcamifen 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.

The highest acute dietary intake was estimated at <1 per cent of the ARfD (women of child-bearing age only). It is concluded that the acute dietary exposure is acceptable.

## 4.8 Recommendations

The following amendments are required to be made to the APVMA MRL Standard.

**Table 5: Amendments to the APVMA MRL Standard**

| Amendments to Table 1 | | | |
|---|---|---|---|
| **Compound** | | **Food** | **MRL (mg/kg)** |
| ADD: | | | |
| Metcamifen | | | |
| MO | 0105 | Edible offal (mammalian) | *0.03 |
| PE | 0112 | Eggs | *0.03 |
| MM | 0095 | Meat (mammalian) | *0.03 |
| ML | 0106 | Milks | *0.03 |
| PO | 0111 | Poultry, edible offal of | *0.03 |
| PM | 0110 | Poultry meat | *0.03 |
| GC | 0651 | Sorghum | *0.01 |

| Amendments to Table 3 | |
|---|---|
| **Compound** | **Residue** |
| ADD: | |
| Metcamifen | Commodities of plant origin: Metcamifen<br>Commodities of animal origin: Sum of metcamifen and 4-(3-methyl-ureido)-benzensulfonamide, expressed as metcamifen |

| Amendments to Table 4 | | | |
|---|---|---|---|
| **Compound** | | **Animal feed commodity** | **MRL (mg/kg)** |
| ADD: | | | |
| Metcamifen | | | |
| AF | 0651 | Sorghum forage (green)[fresh weight] | *0.01 |
| AS | 0651 | Sorghum straw and fodder, dry | *0.01 |

# 5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

## 5.1 Commodities exported and main destinations

Cereal grains (including sorghum) are considered to be major export commodities[2], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated sorghum. Residues in these commodities resulting from the use of EPIVIO C Sorghum Seed Safener may have the potential to unduly prejudice trade.

## 5.2 Overseas registrations and approved label instructions

The Applicant has indicated that safeners such as metcamifen are regulated differently in different countries. So far, metcamifen has approvals in China and USA under the specific country regulations that apply to this type of substance. In the USA metcamifen received approval as a formulation inert in April 2018. In China the most appropriate registration was determined to be under China chemical law, not their pesticide law.

## 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. 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. Metcamifen has not been considered by Codex. No MRLs are established overseas for metcamifen.

## 5.4 Potential risk to trade

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

Residues of metcamifen are not expected in Australian sorghum grain following treatment according to the proposed use pattern. It is considered that there is a low potential risk to trade as residues above the LOQ of 0.01 mg/kg should not occur following use in accordance with label instructions.

MRLs for animal commodities are proposed at the LOQ of 0.03 mg/kg, so the risk to trade in animal commodities is considered to be low.

[2] APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B), apvma.gov.au/node/1017

# 6 WORK HEALTH AND SAFETY ASSESSMENT

## 6.1 Health hazards

In rats, EPIVIO C Sorghum Seed Safener is of low acute oral and dermal toxicity (the oral and dermal LD50s were both >2000 mg/kg bw) and low inhalation toxicity (with an LC50 > 3490 mg/m$^3$). The product is a slight eye irritant but does not cause skin irritation or sensitisation. Based on the use pattern and this acute hazard profile, workers handling and preparing the product would not need to wear personal or respiratory protective equipment.

A NOAEL for assessment of occupationally exposed persons was therefore chosen from among the short-term repeat-dose, sub chronic and developmental toxicity studies with metcamifen. Although the database for metcamifen includes a 28 day study in rats by dermal administration, the NOAEL from a developmental toxicity study in rabbits performed via the oral route was selected, as the lowest NOAEL was based on an end-point not examined in the dermal toxicity study. Adjusting for the incomplete (estimated at 62.4 per cent) oral absorption of metcamifen in rats, the final value of the WHS NOAEL became 18.6 mg/kg bw/d. The acceptable margin of exposure (MOE) from the WHS NOAEL was set at 100 to allow for differences in toxicokinetics, toxicodynamics and sensitivity between and within species.

## 6.2 Occupational exposure

### Exposure during use

EPIVIO C Sorghum Seed Safener is expected to be applied on a seasonal basis, as required by the annual cropping cycle. Consequently, occupational exposure to metcamifen will be discontinuous, occurring repeatedly for up to three months before and at commencement of the sorghum growing season but followed by an extended exposure-free interval between planting and preparations for the next growth season.

Based on exposure monitoring data from persons preparing and applying another seed treatment and handling treated seed under the same conditions of use envisaged for EPIVIO C Sorghum Seed Safener, dermal and inhalation exposure were estimated for seed treaters, baggers, bag sewers and seed planting machine operators. Supplementary estimates of exposure were also made using the Pesticide Handler Exposure Database (PHED). Relative to the workplace health and safety (WHS) NOAEL for repeat-dose toxicity of metcamifen in laboratory animals, the assessment indicated an acceptable margin of exposure (MOE) of greater than 100 for operators mixing/loading and applying the product while wearing coveralls and gloves without respiratory protective equipment. There were also acceptable MOEs for seed baggers, bag sewers and operators of automated seed planting equipment wearing coveralls without additional personal or respiratory protective equipment (PPE or RPE).

### Exposure during re-entry or rehandling

The APVMA did not consider it necessary to estimate MOEs for workers re-entering fields sown with treated seed, because the seeds will be covered by soil immediately after planting and there is negligible likelihood of exposure to residues of metcamifen while performing agricultural activities.

## 6.3 Public exposure

Bystanders and members of the public, are highly unlikely to become exposed to metcamifen during seed treatment or planting operations. Given that EPIVIO C Sorghum Seed Safener is expected to be used only by professional horticulturalists and seed treatment operators, the product is unlikely to enter the public domain except during transport.

## 6.4 Recommendations

The following first aid instructions, safety directions and precautionary (warning) statements are recommended for the product label.

### First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126; New Zealand 0800 764 766.

### Safety directions

Will irritate the eyes. Avoid contact with eyes. When opening the container, mixing, loading and using the prepared seed treatment, wear cotton overalls buttoned to the neck and wrist and a washable hat and elbow-length chemical resistant gloves. If clothing becomes contaminated with product, remove clothing immediately. If product on skin, immediately wash area with soap and water. When handling treated seed, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). After use and handling treated seed, and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves and contaminated clothing.

### Precautionary (warning) statements

No additional label warning statements or general safety precautions are required.

# 7 ENVIRONMENTAL ASSESSMENT

To support the application a full suite of environmental fate and toxicity data were provided for the formulated product, the technical active constituent, and several of its metabolites.

The product is a seed treatment and foraging birds and mammals may be exposed through their diet by feeding on the treated seed, or consuming newly emerged shoots and leaves following germination. Aquatic organisms may be exposed as the result of run-off. Potential exposure of bees, other beneficial arthropods and soil dwelling organisms once the chemical has entered the soil was also considered. Spray drift to natural aquatic areas or vegetation areas is not relevant to this use pattern.

## 7.1 Fate and behaviour in the environment

### Soil

The rate and route of degradation of metcamifen was investigated under aerobic conditions in six laboratory soils incubated in the dark at 20°C for up to 122 days. Degradation was extensive and three major metabolites were identified: sulphonamide metabolite CGA214513 (up to 51 per cent AR), O-desmethyl metabolite CGA277776 (up to 14 per cent) and N-desmethyl metabolite SYN546368 (up to 10 per cent). Up to 46 per cent mineralization to $CO_2$ occurred throughout the incubation period with bound residues ranging 12–40 per cent AR by the end of the study. The aerobic soil degradation half-lives ($DT_{50}$) ranged from 3.5 to 141 days, with a geometric mean $DT_{50}$ of 30 days.

The rate and route of metcamifen was also investigated under anaerobic conditions in four laboratory soils incubated in the dark at 20°C for up to 120 days. Degradation of was extensive with the three major metabolites observed (up to 53 per cent CGA214513, 14 per cent CGA277776, and 15 per cent SYN546368). Mineralization to $CO_2$ reached up to 36 per cent and bound residues ranged 22–35 per cent by the end of the study. The anaerobic soil $DT_{50}$ values ranged from 89 to 309 days, with a geometric mean $DT_{50}$ of 176 days.

In a soil photolysis study under laboratory conditions, metcamifen degraded slowly in both dry and moist soil conditions ($DT_{50}$ 140 and 124 days, respectively). Therefore, photolysis is not considered to be an important degradation pathway in the soil environment.

The adsorption/desorption characteristics of metcamifen were investigated in six soils at 20°C using a standard batch equilibrium method. The calculated Freundlich adsorption coefficients (Kf) ranged from 0.31 to 13 mL/g. Following correction of the Kf values for the soil organic carbon content, Kfoc values ranged from 26 to 463 mL/g with an arithmetic mean Kfoc of 159 mL/g. There was not a statistically significant relationship between soil sorption and organic carbon content. However, a relationship between sorption and soil pH was demonstrated with decreasing sorption as soils become more alkaline.

The persistence and mobility of metcamifen and its major soil metabolites CGA214513, CGA277776, and SYN546368 was investigated in two terrestrial field soil dissipation trials conducted in the United States (Georgia and Nebraska). In both trials, residues of metcamifen remained predominately in the top 7.5 cm of soil. Downward movement of the major metabolites was negligible below the top 30 cm. The field soil $DT_{50}$

values for metcamifen were 32 days (Georgia) and 60 days (Nebraska), with a geometric mean $DT_{50}$ of 44 days.

### Water

In laboratory studies, metcamifen was stable to hydrolysis but photolysis was very fast with $DT_{50}$ values of 7.9 hours (pH 7 buffer) and 6.6 hours (natural water) in summer sunlight at 30 to 50 °N. Four major photoproducts were observed: SYN546367 (up to 67 per cent), SYN546366 (up to 26 per cent), CGA169292 (up to 11 per cent) and CGA83833 (up to 38 per cent).

The rate and route of degradation of metcamifen was investigated in two different water-sediment systems, Swiss Lake (sand) and Calwich Abbey (silt loam), maintained under aerobic and anaerobic conditions at 20°C in the dark for 100 to 102 days. Up to 23 per cent metcamifen partitioned to the sediment by the end of the study. Two major metabolites were observed in both the water and sediment phases: CGA277776 and CGA214513 (up to 26 per cent and 13 per cent in the total systems, respectively). Mineralisation (up to 14 per cent) and bound residues (13 to 16 per cent) were relatively low by the end of the study. The $DT_{50}$ values for metcamifen were 49 to 69 days in the water phase and 68 to 121 days in the total system, with a geomean $DT_{50}$ of 91 days in the total system. The fate and behaviour of metcamifen was similar between aerobic and anaerobic systems.

### Air

Given its vapour pressure of $<6.3 \times 10^{-6}$ Pa and the Henry's law constant of $<1.14 \times 10^{-6}$ Pa m³/mol at 25ºC, volatilisation of metamifen from soil and plant surfaces is unlikely. The rate of reaction of metcamifen in the atmosphere with hydroxyl radicals was estimated to be $DT_{50}$ 3.5 hours, indicating long-range transport through the air is not expected.

## 7.2 Effects and associated risks to non-target species

### Terrestrial vertebrates

Following gavage administration, metcamifen had low toxicity to mammals ($LD_{50}$ >5000 mg ac/kg bw, *Rattus norvegicus*) and birds ($LD_{50}$ >2000 mg ac/kg bw, *Colinus virginianus*). Metcamifen had similarly low toxicity to birds following short-term dietary exposure (LC50 >5620 mg ac/kg diet, two species tested). Following long-term dietary administration in reproduction studies, there were treatment related effects on egg fertility and embryo viability of birds at the highest treatment rate of 726 mg ac/kg bw/d (NOEL 129 mg ac/kg bw/d, *Anas platyrhynchos*), while there were no effects in either the parental or filial generations of mammals at the highest dose (NOEL 191 mg ac/kg bw/d, *Rattus norvegicus*).

The risk to mammals and birds was determined using standard assessment approaches for estimating exposure from treated seed and comparing to the known acute and chronic toxicity to birds and mammals. In all cases, the risk was found to be acceptable.

## Aquatic species

Metcamifen has low toxicity to fish ($LC_{50}$ >96 mg/L, four species tested), moderate toxicity to aquatic invertebrates (lowest $EC_{50}$ 12 mg ac/L, *Crassostrea virginica*), moderate toxicity to algae (lowest $E_rC_{50}$ 34 mg ac/L, *Anabaena flos-aquae*) and low toxicity to aquatic plants ($E_rC_{50}$ >94 mg/L, *Lemna gibba*). Following long-term exposure, metcamifen had no effects in the early life stages of fish up to the maximum rate of 11 mg ac/L (*Pimephales promelas*), or on the survival or reproduction of aquatic invertebrates at a maximum concentration of 103 mg ac/L (*Daphnia magna*). Available data indicate that the major metabolites CGA214513 and CGA277776 have low toxicity to fish ($LC_{50}$ >100 mg/L) and aquatic invertebrates ($EC_{50}$ >100 mg/L). The risk of metcamifen to aquatic species was shown to be acceptable in a worst-case scenario of direct exposure.

## Bees and other non-target arthropods

Metcamifen has low toxicity to adult bees (*Apis mellifera*) by contact exposure ($LD_{50}$ >100 µg ac/bee) and oral exposure ($LD_{50}$ >67 µg ac/bee) and to bee larvae ($LD_{50}$ >3.3 µg ac/bee). Following long-term dietary administration, no adverse effects were observed in adult or larval bees at the highest test concentration (NOEL 2.9 and 7.4 µg ac/bee/d, respectively). No information was available on the translocation behaviour of metcamifen in plants following seed treatment; therefore, the risk assessment assumed the worst-case scenario of residues being transported to pollen and nectar of the plant. The risk of metcamifen to bees was shown to be acceptable in this worst-case scenario.

Data have also been provided addressing the contact toxicity of fresh-dried residues of metcamifen to two indicator species of beneficial arthropods *Typhlodromus pyri* and *Aphidius rhopalosiphi*. The studies provided were Tier 1 (glass plate) studies with $LR_{50}$ values >400 g ac/ha for both species. The risk of metcamifen to beneficial arthropod species was shown to be acceptable in a worst-case scenario of direct exposure to fresh-dried residues.

## Soil organisms

Metcamifen has low toxicity to soil macro-organisms such as earthworms ($LC_{50}$ >1000 mg ac/kg dry soil, *Eisenia fetida*). Following long-term exposure in soil, metcamifen did not inhibit reproduction at exaggerated soil concentrations (NOEC 1000 mg ac/kg soil, *Eisenia fetida*). The effects of metcamifen on soil processes such as nitrogen transformation was extrapolated based on toxicity testing with other microbial communities in an activated sludge inhibition test and comparing to predicted soil pore water concentrations. The risk of metcamifen to soil organisms was shown to be acceptable in a worst-case scenario of direct exposure.

## Non-target terrestrial plants

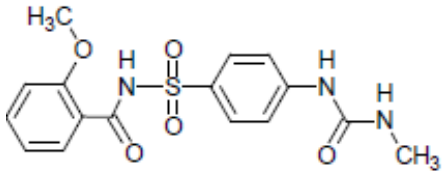
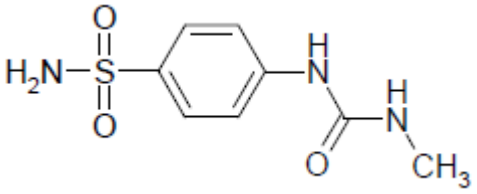
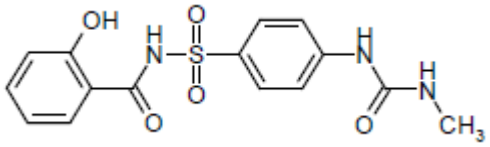
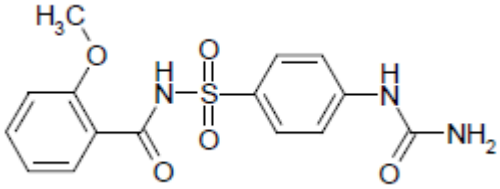
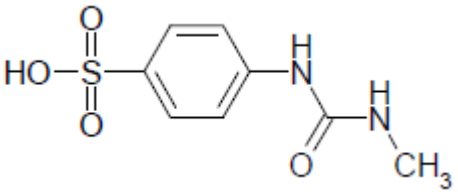
Tier 1 (limit) testing of an SC formulation of metcamifen at 200 g ac/ha on ten crop species in pre- and post-emergent tests showed <25 per cent effect on all species with the exception of 26 per cent inhibition in *Allium cepa* in the seedling emergence study. Assuming up to eight kilograms of treated sorghum seed is planted per hectare, this equates to a soil exposure rate of 8.0 g ac/ha. Considering only a marginal impact at highly exaggerated rates, the risk to non-target terrestrial plants was considered acceptable.

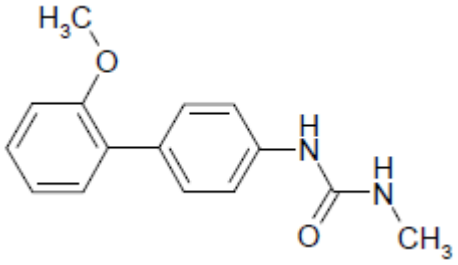
## 7.3 Recommendations

Based on the outcome of the risk assessment, the proposed use of EPIVIO C Sorghum Seed Safener is not, or would not be, likely to have an unintended effect that is harmful to animals, plants or things or to the environment following use in accordance with label instructions.

## 7.4 Residues relevant to the environment

**Table 6: Residues relevant to the environment**

| Identifier | Structure |
|---|---|
| Metcamifen |  |
| CGA214513 |  |
| CGA277776 |  |
| SYN546368 |  |
| SYN546366 |  |

| Identifier | Structure |
|---|---|
| SYN546367 |  |

# 8 EFFICACY AND SAFETY ASSESSMENT

## 8.1 Proposed product use pattern

The product EPIVIO C Sorghum Seed Safener, containing 400 g/L metcamifen is proposed for the protection of grain and forage sorghum from the phytotoxic effects of soil applied S-metolachlor.

## 8.2 Efficacy and target crop/animal safety

The applicant has provided a comprehensive dossier of 19 studies conducted in major Australian sorghum growing areas over three years in support of registration of EPIVIO C Sorghum Seed Safener, for the protection of grain and forage sorghum from the phytotoxic effects of soil applied S-metolachlor. The trials were designed and conducted in an appropriate scientific fashion. The treatments were appropriate for evaluating the efficacy and crop safety of the earlier formulation A18575F and EPIVIO C Sorghum Seed Safener at three rates, which were compared to the existing commercial standard Concep II at the label rate. The test herbicide was Dual Gold (containing S-metolachlor) at the maximum label rate of 2 L/ha (1920 g ac/ha).

### Efficacy

The sorghum crop situations were generally managed according to standard practice. The confounding effects of weed growth were minimised by use of other standard herbicides (eg atrazine), or in some trials by hand weeding. Assessments were made of crop establishment, plant growth and plant health (phytotoxicity), and in the final year also yield. The A18575F formulation tested in the trials in the first year (2015–16) was shown in subsequent trials to be bioequivalent in efficacy to EPIVIO C Sorghum Seed Safener at the same rate of active constituent (100 g ac/100 kg seed).

### Crop safety

No noticeable effect on emergence relative to untreated and/or safened seed plots resulted in six experiments, in five of these cases associated with very low or no rainfall or irrigation in the period following herbicide application. In the other 13 trials, effective protection of sorghum seed from the harmful effects of Dual Gold on crop establishment was demonstrated in plots established with EPIVIO C Sorghum Seed Safener applied at 250 mL/100 kg or A-18575 applied at 500 mL/100 kg seed, with significant differences evident compared to unsafened seed. The results support the proposed rate of 250 mL. In all experiments where there were significant differences in establishment, EPIVIO C Sorghum Seed Safener applied at 250 mL/100 kg or A-18575-F gave equal to or better establishment compared to plots established using Concep II. These conclusions are generally supported by the results from other assessments.

## 8.3 Recommendations

The results with either A18575F or EPIVIO C Sorghum Seed Safener applied at the proposed use rate on sorghum seed without PSPE Dual Gold application found no crop safety concerns across the six sorghum cultivars tested.

# 9 LABELLING REQUIREMENTS

**READ SAFETY DIRECTIONS BEFORE OPENING OR USING**

Epivio® C
Sorghum Seed Safener

syngenta®

**ACTIVE CONSTITUENT: 400 g/L METCAMIFEN**

*For application to Sorghum Seed as a seed treatment to protect it from the phytotoxic effects of Dual® Gold Herbicide and Primextra Gold® Herbicide*

# f500 mL to 100 LITRES

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

**APVMA Approval No: 87317/118088**
**Item no.**

## DIRECTIONS FOR USE

**Restraints**
Treated seed must be clearly labelled “EPIVIO C treated for Dual Gold Herbicide and Primextra Gold Herbicide pre-emergent weed control” and carry the warning: ‘DO NOT feed to animals’.

| Crop | Action | Rate | Critical Comments |
|---|---|---|---|
| **Sorghum** | Protects planted crop from injury when Dual Gold and Primextra Gold are applied at recommended label rates. | 250mL/ 100 kg of seed | **Commercial Seed Treatment**<br>Apply diluted with water to clean /healthy seed before sowing. Thorough mixing is required to ensure complete coverage. Coverage of all seeds is essential.<br>Allow seed to dry before bagging.<br><br>**Individual Bag Treatment**<br>Place bag (20 kg) of sorghum seed into cement mixer or similar treatment equipment. Whilst rotating slowly and evenly apply 50 mL of EPIVIO C diluted with water and continue rotation for 1 to 2 minutes or until adequate coating is observed. |

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

## WITHHOLDING PERIODS

***Sorghum:*** **Harvest: NOT REQUIRED WHEN USED AS DIRECTED**
**Grazing: DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 6 WEEKS AFTER PLANTING**

## GENERAL INSTRUCTIONS

The product is used as a seed treatment to protect grain or forage sorghum from the phytotoxic effects of S-metalochlor herbicides. Protects planted crop from injury when Dual Gold and/or Primextra Gold are applied at recommended rates.

**Application:**
***Treatment in small lots by the farmer***
May be applied to seed in an enclosed drum or cement mixer.
1. Premix EPIVIO C with water to a total volume of not less than 800 mL nor more than 1.6 L/100 kg seed.
2. Apply solution to seed and vigorously mix for 1 to 2 minutes.

***Treatment of large seed lots by commercial seed treatment equipment***
For large scale seed treatment the product should be applied diluted with water in specialised seed treatment equipment. As for all such seed treatments, a good flow and metering system for the initial prepared solution is important. Depending on the type of seed treatment equipment and additional products being applied in slurry, it may be necessary to adjust the recommended amount of water and total volume in order to ensure an optimal flow of the solution and an even treatment of seed.

Prepare the solution as follows:

1. Fill the solution tank with the required volume of water and mix with the appropriate volume of EPIVIO C. Total volumes of not less than 800 mL nor more than 1.6 L/100 kg seed are recommended when applying alone. When applied with other seed treatments products, higher total volumes can be applied to ensure optimal flow of slurry solution and even coverage of seed.
2. Switch on the stirring system and stir.

## PRECAUTIONS

DO NOT use treatment seed for animal or human consumption.

DO NOT allow treated seed to contaminate grain/other seed intended for animal or human consumption.

DO NOT feed treated seed, or otherwise expose, to wild or domestic birds.

Any spillage of treated seed which occurs either during the seed treatment process or in the field operations must be cleaned up immediately, preferably by recover and re-use. If disposal is required, ensure treated seeds are thoroughly buried and not accessible to birds and other wildlife.
When treated seed is stored it should be kept apart from other grain and the bags or other containers should be clearly marked to indicate the contents have been treated. Bags which have held treated seed should not be used for any other purpose.

## PROTECTION OF LIVESTOCK

DO NOT feed treated seed to animals, including poultry.

## PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

DO NOT contaminate wetlands or watercourses with this product or used containers.

## STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well ventilated area. DO NOT store for prolonged periods in direct sunlight.
Triple-rinse containers before disposal. Add rinsings to mixing tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant local, state or territory government regulations. DO NOT burn empty containers or product.

## SAFETY DIRECTIONS

May irritate the eyes. Avoid contact with eyes. When opening the container, mixing, loading and using the prepared seed treatment, wear:

- cotton overalls buttoned to the neck and wrist
- a washable hat
- elbow-length chemical resistant gloves.

When bagging treated seed, wear:

- cotton overalls buttoned to the neck and wrist (or equivalent clothing).

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

## FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone 131 126

## SAFETY DATA SHEET

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

## DISCLAIMER

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



| | |
|---|---|
| Batch No | |
| Date of Manufacture | |

# ABBREVIATIONS

| | |
|---|---|
| ac | active constituent |
| ADI | Acceptable Daily Intake (for humans) |
| ai | active ingredient |
| ARfD | Acute Reference Dose |
| bw | bodyweight |
| d | day |
| DAT | Days After Treatment |
| $DT_{50}$ | Time taken for 50% of the concentration to dissipate |
| $EC_{50}$ | concentration at which 50% of the test population are immobilised |
| $E_rC_{50}$ | concentration at which the rate of growth of 50% of the test population is impacted |
| EI | Export Interval |
| EGI | Export Grazing Interval |
| ESI | Export Slaughter Interval |
| g | gram |
| GAP | Good Agricultural Practice |
| h | hour |
| ha | hectare |
| IPM | Integrated Pest Management |
| in vitro | outside the living body and in an artificial environment |
| in vivo | inside the living body of a plant or animal |
| kg | kilogram |
| L | Litre |
| $LC_{50}$ | concentration that kills 50% of the test population of organisms |
| $LD_{50}$ | dosage of chemical that kills 50% of the test population of organisms |
| LOD | Limit of Detection—level at which residues can be detected |
| 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 |
| MSDS | Material Safety Data Sheet |
| NEDI | National Estimated Daily Intake |
| NESTI | National Estimated Short Term Intake |
| ng | nanogram |
| NOEC/NOEL | No Observable Effect Concentration Level |
| NOAEL | No Observed Adverse Effect Level |
| ppb | parts per billion |
| PPE | Personal Protective Equipment |
| ppm | parts per million |
| Q-value | Quotient-value |
| REI | Re-Entry Interval |
| s | second |
| SC | Suspension Concentrate |
| SUSMP | Standard for the Uniform Scheduling of Medicines and Poisons |
| TGA | Therapeutic Goods Administration |
| TGAC | Technical grade active constituent |
| µg | microgram |
| 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 |

# REFERENCES

APVMA 2015, *Data Guidelines,* Australian Pesticides and Veterinary Medicines Authority, Canberra, available at apvma.gov.au/registrations-and-permits/data-guidelines.

WHO 1997, *Guidelines for predicting dietary intake of pesticide residues*, World Health Organization, Geneva, available at: who.int/foodsafety/publications/pesticides/en/.