Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Constituent **Halauxifen-methyl**

in the Product **GF-2685 Herbicide**

APVMA Product Number 65055

DECEMBER 2014

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This document is published by the APVMA. In referencing this document the APVMA should be cited as both author and publisher.

ISSN: 1443-1335
ISBN: 978-1-922188-79-3

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

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PREFACE

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

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

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

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes.

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of GF-2685 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 **Tuesday 27 January 2015** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

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

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

Case Management and Administration Unit
Registration Management and Evaluation
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4700
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

Further information

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

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

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

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

1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of GF-2685 Herbicide, and approval of the new active constituent, Halauxifen-methyl.

This submission has been assessed under a joint review/ workshare arrangement where registrations for the same formulations and uses have been submitted concurrently in Australia, Canada and the USA.

It is proposed to register GF-2685 Herbicide, a water dispersible granule (WG) formulation containing 100 g/kg halauxifen present as the methyl ester. Halauxifen-methyl is a new herbicide for the control of annual broadleaf weeds in wheat and barley. GF-2685 Herbicide is formulated with halauxifen-methyl and the crop safener cloquintocet-mexyl.

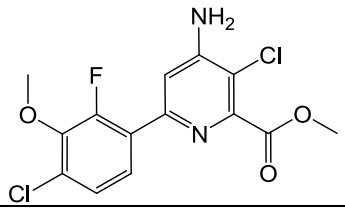
Halauxifen-methyl is the first member of a new chemical class of synthetic auxin herbicides, the arylpicolinates. Halauxifen-methyl mimics the effect of a persistent high dose of the natural plant hormone auxin, causing over-stimulation of specific auxin-regulated genes which result in the disruption of several growth processes in susceptible plants. For weed resistance management, GF-2685 is a Group I Herbicide.

Halauxifen-methyl is currently registered in products in Canada for control of annual broadleaf weeds in spring and winter wheat, durum wheat and spring barley.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

Chemical Characteristics

COMMON NAME:	Halauxifen-methyl
IUPAC NAME:	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate
CAS NAME:	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-2-pyridinecarboxylate
CAS REGISTRY NUMBER:	943831-98-9
MANUFACTURER'S CODES:	XDE-729 methyl
MINIMUM PURITY:	930 g/kg
MOLECULAR FORMULA:	$C_{14}H_{11}Cl_2FN_2O_3$
MOLECULAR WEIGHT:	345.15 g/mol
STRUCTURE:	
CHEMICAL FAMILY:	pyridine carboxylic acid family
MODE OF ACTION:	It binds to protein receptor sites that normally regulate plant processes. Halauxifen-methyl is rapidly absorbed by the leaves and roots, moves systemically throughout the target plant in the xylem and phloem and accumulates in the meristematic tissue, where it deregulates growth metabolic pathways.

Manufacturing Site:

The Dow Chemical Company, Michigan Division, Midland, Michigan 48640, USA

APVMA Active Constituent Standard for Halauxifen-methyl Active Constituent

CONSTITUENT	SPECIFICATION	LEVEL
Halauxifen-methyl	Halauxifen-methyl	Not less than 930 g/kg

Physical and Chemical Properties of Active Constituent

PHYSICAL STATE	White to off white powder	
ODOUR	Mild	
MELTING POINT	145.5°C	
BOILING POINT	Decomposes before boiling	
RELATIVE DENSITY	Density: 1.5418 g/cm^3 at 20.5 °C Bulk density: 0.17 g/mL at 25.2 °C	
pH OF 1%	6.24 (1% suspension in distilled water at 25. °C)	
SOLUBILITY IN WATER	pH	solubility (mg/L) at 20°C
	purified water	1.83
	5	1.66
	7	1.67
	9	1.69
SOLUBILITY IN VARIOUS SOLVENTS AT 20°C	TGAI (g/L) at 20 °C	
	Methanol	38.1
	Acetone	>250
	Xylene	9.13
	1,2-dichloroethane	65.9
	Ethyl acetate	129
	n-heptane	0.0361

	n-octanol	9.83
VAPOUR PRESSURE	Pure active ingredient 1.5 x 10^{-8} Pa at 25°C (1.1 x 10^{-10} mm Hg) 5.9 x 10^{-9} Pa at 20°C (4.4 x 10^{-11} mm Hg)	
HENRY'S LAW CONSTANT	pH	Henry's law constant
	unbuffered	1.11 x 10-6 Pa m3/mol
	5	1.23 x 10-6 Pa m3/mol
	7	1.22 x 10-6 Pa m3/mol
	9	1.20 x 10-6 Pa m3/mol
N-OCTANOL/WATER PARTITION COEFFICIENT	pH	Log Kow at 20˚C
	5	3.75
	7	3.76
	9	3.92
HYDROLYSIS RATE AT 25˚C	pH	Hydrolysis
	4	Halauxifen acid (maximum 23.7% of applied); DT50: 80.9 days
	7	Halauxifen acid (maximum 13% of applied); DT50: 155 days
	9	Halauxifen acid (maximum 99.3% of applied); DT50: 3.04 days

PHOTO-STABILITY	Halauxifen-methyl dissipated in irradiated solutions with half-lives of 0.003 days in pH 7 buffer and 0.004 days in natural water (4.3 and 6.9 minutes, respectively). In the dark controls, halauxifen-methyl dissipated with half-lives of 158 days in pH 7 buffer and 7.4 days in natural water. The overall mass balance was 87.5–101.4% of the applied in the irradiated solutions and 98.9–102.2% in the dark controls. Identity of breakdown products: numerous photoproducts and carbon dioxide.
DISSOCIATION CONSTANT (pKa)	pKa: 2.84 ± 0.04 at 19.9°C
UV/VIS ABSORPTION (MAX.) IN ACETONITRILE SOLVENT	medium λ max, nm Neutral: 212, 249 Acidic: 215, 256 Basic: 212, 247
FLAMMABILITY	Not highly flammable
AUTO- FLAMMABILITY	No self-ignition temperature under the conditions of the test
EXPLOSIVE PROPERTIES	Not explosive
OXIDISING PROPERTIES	Not oxidizing

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of halauxifen-methyl are acceptable.

2.2 Product

DISTINGUISHING NAME:	GF-2685 Herbicide
FORMULATION TYPE:	Water Dispersible Granule (WG)
ACTIVE CONSTITUENT CONCENTRATION:	Halauxifen-methyl(100 g/kg) and Cloquintocet-mexyl (100 g/kg)

The product GF-2685 Herbicide will be manufactured overseas and imported into Australia in 1 kg to 10 kg high density polyethylene (HDPE) containers or 500 g to 5 kg foil satchels.

PHYSICAL AND CHEMICAL PROPERTIES OF THE PRODUCT

PROPERTY	Results
APPEARANCE	Tan solid
PH VALUE	5.8 on 1% aqueous dilution
BULK DENSITY	0.57 g/mL
SPECIFIC GRAVITY	Not applicable
SURFACE TENSION	Not applicable
VISCOSITY	Not applicable
EXPLOSIVE PROPERTIES	Not explosive
OXIDISING PROPERTIES	Not oxidising
FLAMMABILITY	Not applicable
CORROSIVE HAZARD	Not corrosive to HDPE containers
PERSISTENT FOAM	<60 mL foam after 1 minute
WET SIEVE TEST	<2% residue on a 75 micron sieve
PARTICLE SIZE DISTRIBUTION	88.5% between 250 and 500 micron 82.3% with more particles in larger and smaller sieves 97.6% with fewer particles in larger sieve
WETTABILITY	Wet <3 seconds
SUSPENSIBILITY	Between 60 and 105%
SPONTANEITY OF DISPERSION	99%
DUST CONTENT	Nearly dust free (3.6 mg)
FRIABILITY AND ATTRITION CHARACTERISTICS OF GRANULES	100% attrition resistance
FLOWABILITY	Sample flowed through the 4.75 mm sieve after 5 liftings
PACK SIZES	500g, 1 kg, 5 kg, 10 kg

PACKAGING MATERIAL	High density polyethylene (HDPE) and foil satchel
PRODUCT STABILITY	The product should remain within specifications for at least 2 years under normal conditions in HDPE packaging

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of GF-2685 Herbicide are acceptable.

3 TOXICOLOGICAL ASSESSMENT

The toxicology database for halauxifen-methyl is extensive and comprehensive.

Toxicokinetic data from guideline studies in mice and rats and included in toxicological studies in rodents demonstrated rapid hydrolysis of halauxifen-methyl to halauxifen acid, and demonstrated systemic exposure following oral dosing to be to halauxifen acid. Additionally, based on an in vivo dermal absorption study in rats on a product containing halauxifen-methyl it is considered that systemic exposure following application of halauxifen-methyl via the dermal route would be to halauxifen acid.

The complete database of toxicology studies were therefore conducted on halauxifen acid, with bridging studies (six packs of acute studies, rat short term, rat subchronic, rat and rabbit developmental, genotoxicity, metabolism, and immunotoxicity) in addition to mechanistic in vitro, in vivo and in situ PBPK modelling data for mode of action (MOA) analysis performed on halauxifen-methyl. The toxicology studies were conducted in accordance with contemporary test guidelines.

The toxicological database was considered to be adequate for establishing a toxicological profile and sufficient for regulatory purposes.

In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are generally used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans would be expected.

3.1 Chemical Class

Halauxifen-methyl (also known as XDE-729 methyl) is the first member of a class of new synthetic auxin herbicides, the arylpicolinates. It produces auxin-type response in susceptible annual broadleaf weeds.

3.2 Metabolism and toxicokinetics

Evaluation of the available metabolism and toxicokinetic data indicated that radiolabelled halauxifen-methyl fed to rats was rapidly and completely absorbed from the gastrointestinal tract. Halauxifen-methyl is rapidly and extensively converted to halauxifen acid following oral dosing in mice, rats and dogs. Repeat dose oral toxicity studies demonstrate pre-systemic exposure to halauxifen-methyl in the liver across species; however, the available toxicokinetic and toxicological data indicate that systemic exposure is to halauxifen acid. Distribution of the radiolabel was extensive with no evidence of bioaccumulation in tissues following single and

repeat oral exposure in rats. The majority of the administered dose of halauxifen-methyl or acid in rats and halauxifen acid in dogs was excreted within 24 hours in the urine as halauxifen acid and some minor metabolites, with a small percentage excreted in faeces.

An in vivo dermal absorption study in rats on a product containing halauxifen-methyl demonstrated that the halauxifen-methyl in the product was completely hydrolysed to halauxifen acid as identified in measurements of blood taken at 4 and 10 hours post application. Overall it was considered that systemic exposure following application of halauxifen-methyl via the dermal route would be to halauxifen acid.

3.3 Acute toxicity

Based on the findings of the acute toxicological studies evaluated, halauxifen-methyl and halauxifen acid are of low acute oral and dermal toxicity. A waiver request for acute inhalational toxicity studies on halauxifen-methyl and halauxifen acid was accepted based on inability to generate a guideline-compliant respirable dry powder aerosol and are not considered to be acute inhalational hazards. Halauxifen-methyl and halauxifen acid are not skin irritants in rabbits or skin sensitisers in mice (LLNA). Halauxifen-methyl and halauxifen acid are non-irritating and slightly irritating to the eyes of rabbits, respectively.

Based on the findings of the acute toxicological studies on GF-2685 herbicide, the product is of low acute oral, dermal and inhalational toxicity in rats, and has slight irritation to the eyes and skin of rabbits. However, in the absence of an acceptable guideline skin sensitisation study on the product it is considered to have positive potential of skin sensitisation based on the constituents in the product and their concentrations.

3.4 Systemic toxicity

Short-term to chronic oral studies with mice, rats and dogs administered halauxifen acid demonstrated the kidney to be the target organ of toxicity with effects on urinalysis and clinical chemistry parameters and correlating histopathological changes including urinary bladder and renal tubules. These findings do not warrant scheduling.

Short-term to subchronic oral studies in rats with halauxifen-methyl demonstrated that the most sensitive endpoint of toxicity was the liver, and was observed at doses lower than doses of halauxifen acid causing kidney toxicity in short-term and subchronic studies in mice, rats and dogs. The applicant has proposed a pre-systemic Mode of Action (MOA) in rodents to address the different toxicity profiles between halauxifen-methyl and halauxifen acid in rodents following repeat-dosing.

Mode of Action

Halauxifen-methyl induces rodent liver effects via a proposed aryl hydrocarbon receptor-mediated mode of action (MOA) through the following key events (1) pre-systemic liver exposure to halauxifen-methyl, (2) aryl hydrocarbon receptor (AhR) activation with associated liver weight increase and hepatocyte hypertrophy, leading to (3) hepatocellular proliferation. These key events have been supported by guideline short-term and a subchronic oral toxicity studies in rats (including gene expression analyses of liver enzymes), MOA short-term in vivo studies in mice and rats and mechanistic in vitro studies in mice, rat and human cell lines, aimed at characterizing the MOA for halauxifen-methyl-mediated liver effects. Toxicokinetic studies and toxicokinetic

data from guideline short-term and subchronic studies, and short-term in vivo MOA data and metabolism data from in vitro mechanistic demonstrate that halauxifen-methyl is rapidly hydrolysed to halauxifen acid as the major metabolite for systemic exposure. Standard guideline 90–Day toxicity studies with halauxifen-methyl and MOA short-term in vivo studies (7 and 28 Day) in rats demonstrated a dose related increase in liver quantification of halauxifen-methyl (pre-systemic exposure) at low levels, with no evidence of bioaccumulation. Halauxifen acid has been shown through both in vitro and in vivo assays not to induce AhR activation and associated liver responses. Therefore, the MOA/HRF analysis is focused on halauxifen-methyl induced AhR-mediated effects in the liver from pre-systemic exposure.

Target liver enzyme data in the 90–Day study in rats and short-term in vivo mechanism of action studies (7 or 28 days) in rats demonstrated pre-systemic exposure of the rodent liver to halauxifen-methyl activating the AhR signalling pathway as indicated by a robust and dose-responsive induction in Cyp1a1(sensitive biomarker of AhR activation) with correlating increased mitotic figures/BrdU labelling index indicative of hepatocellular proliferation (7–28 Day studies), gross- and histo-pathological findings in the liver and increased Ugt1a6 (thyroid hormone) liver transcript levels correlating to secondary (liver induction) histopathological findings in the thyroid in rats fed halauxifen-methyl but not in rats fed halauxifen acid. Importantly, liver effects (i.e., measureable apical end points) occurred at doses ≥50 mg/kg bw/day halauxifen-methyl with a clear threshold for liver effects at a no-observed-adverse-effect level (NOAEL) of 10 mg/kg bw/day and corresponding Cyp1a1 induction of > 600 fold in short-term studies in rats and >1000 fold in the 90–Day study in rats. In the 28–Day MOA study in rats all endpoints of AhR-mediated liver toxicity were reversible within 4 and 28–Days of recovery. Analyses of the temporal relationship at comparable doses across 28–Day and 90–Day studies in male rats did not provide evidence of an increase in Cyp1a1 induction (sensitive biomarker for AhR activation) and the severity and/or incidence of liver weights and hepatocellular hypertrophy was comparable in 28 and 90–Day studies in rats. Further hepatocellular proliferation as measured by increased mitotic figures in 7, 28, and 90–Day toxicity studies in rats and additionally by BrdU labelling in the 28–Day MOA study in rats demonstrated increased proliferation at or above threshold dose of ~50 mg/kg bw/day in 7 and 28–Day studies but was absent in the 90-Day study in rats, indicating halauxifen-methyl pre-systemic liver exposure does not result in sustained activation of the AhR signalling pathway and associated hepatocellular proliferation (required for the development of neoplastic changes in the liver).

Several in vitro studies for AhR receptor activation were also completed as part of the assessment of human relevance. Additional supporting events for an AhR-mediated MOA for hepatocellular effects include ligand binding to the receptor, and a series of in vitro assays, which have collectively indicated that halauxifen-methyl is a weak AhR agonist but not halauxifen acid.

The data from these evaluations provides a high level of confidence that halauxifen-methyl induces rodent liver effects through an AhR-mediated MOA.

The rodent MOA data and in vitro mechanistic studies including PBPK modelling provide evidence that humans would be significantly less sensitive than rat to halauxifen-methyl based on the following: 1) kinetic analysis of halauxifen-methyl indicated this molecule is rapidly hydrolyzed to halauxifen by human liver S9 and does not bioaccumulate in rat liver tissues in which hydrolysis is substantially slower, 2) in vitro transactivation and binding assays with halauxifen-methyl indicated that this molecule was a relatively weak ligand for rodent AhR and does not induce sustained activation of the signalling pathway and had no transactivation activity for human AhR, 3) at concentrations of halauxifen-methyl that elicited substantial induction of Cyp1a1 transcript levels in the rat, primary human hepatocytes had minimal induction of CYP1A1 and CYP1A2.

Additionally, it is noted that while the NOAEL of 10 mg/kg bw/d in short-term and subchronic studies in rats were associated with a 7.7 fold Cyp1a1 induction and a 51–148 fold Cyp1a1 induction respectively, there were no associated histopathological changes or liver weight changes. Furthermore, considering the available data demonstrating increased metabolism in humans and a much lower sensitivity to pre-systemic activation of the AhR signalling pathway, the induction at 10 mg/kg bw/d was not considered to be toxicologically significant and, hence, was identified as a NOAEL.

The observed systemic findings (such as liver weight increase and hepatocyte hypertrophy and hepatocellular proliferation) following oral administration of halauxifen-methyl do not warrant scheduling.

In a short-term dermal toxicity study in rabbits halauxifen acid there were no treatment related effects up to the highest dose tested of 1000 mg/kg bw/d.

3.5 Carcinogenicity

Carcinogenicity studies in mice and rats with halauxifen acid did not reveal any treatment related neoplastic changes. Additionally, considering the above genotoxicity data and systemic toxicity data including MOA data and PBPK modelling, halauxifen-methyl is not considered to be a carcinogenic hazard to humans.

3.6 Genotoxicity

Genotoxicity assays for gene mutation in vitro in bacterial cells and mammalian cells, and cytogenetic assays in vitro in rat and human peripheral lymphocytes were negative with and without metabolic activation for both halauxifen-methyl and halauxifen acid. Additionally, an in vivo cytogenetic assay in mice peripheral erythrocytes with halauxifen acid was negative.

3.7 Reproductive and developmental toxicity

Halauxifen acid was not a reproductive toxicant in a rat 2–generation study.

In developmental studies with halauxifen acid in rats and rabbits, foetotoxicity was only observed in rats (decreased foetal body weight and delayed ossification) at a maternotoxic dose of 526 mg/kg bw/d causing increased mortality, decreased gravid uterine weights, increased kidney weight, clinical signs, and decreased body weight gain and food consumption in dams, and is considered a secondary non-specific consequence of such. In developmental studies in rabbits, no foetotoxicity was observed up to and including maternotoxic doses.

In developmental studies with halauxifen-methyl in rats and rabbits, foetotoxicity was only observed in rabbits (decreased foetal body weight and delayed ossification of the pubis) and at the maternotoxic dose of 71.6 mg/kg bw/d causing liver toxicity, including histopathological changes in does, and was considered a secondary non-specific consequence of such.

3.8 Neurotoxicity

Acute and subchronic neurotoxicity studies with halauxifen acid in rats did not reveal any neurobehavioural or neurohistopathological changes up to the highest dose tested.

3.9 Immunotoxicity

Halauxifen-methyl was not immunotoxic in rats, and there was no evidence of an immunotoxic potential in rodent repeat dose oral studies with halauxifen acid.

3.10 Metabolites

Genotoxicity assays for gene mutation in vitro in bacterial cells and mammalian cells, and a cytogenetic assay in vitro in human peripheral lymphocytes were negative with and without metabolic activation for the metabolite X11449757.

3.11 Public Health Standards for halauxifen-methyl

Poisons Scheduling

On the 3rd July 2014, the delegate to the Secretary of the Department of Health made a delegate only decision on halauxifen-methyl (XDE-729 methyl) that it does not require scheduling and therefore should be included in Appendix B of the Standard for the Uniform Scheduling of Medicines and Poisons, along with an implementation date of 1st October 2014.

NOEL/ADI

The acceptable daily intake (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 NOEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The active constituent halauxifen-methyl is rapidly hydrolysed to halauxifen acid and systemic exposure is to the major metabolite halauxifen acid. Therefore the toxicological database for halauxifen-methyl consists of a complete toxicological database for halauxifen acid for which the critical effect is kidney toxicity. However, short-term and subchronic repeat dose toxicity data in mice and rats, including in vivo and in vitro MOA data demonstrate the critical health effect for halauxifen-methyl to be pre-systemic liver exposure resulting in activation of the AhR receptor and subsequent liver toxicity at doses lower than systemic doses of halauxifen acid causing kidney toxicity.

From the toxicological database the lowest available NOAEL is 5.8 mg/kg bw/d for maternal liver toxicity from a developmental study in rabbits with halauxifen-methyl. OCS notes that in the developmental studies the

maternal toxicity data indicate that rabbits may be more sensitive to halauxifen-methyl liver toxicity. In rabbits a NOAEL and LOAEL was observed at 5.8 and 18.5 mg/kg bw/d respectively, whereas the NOAEL and LOAEL for halauxifen-methyl administered to rats was 40.1 and 159 mg/kg bw/d respectively for liver toxicity respectively. Noting that no toxicokinetic or repeat dose oral studies are available in the rabbit and are not standard studies undertaken for determining the human health risk to agricultural pesticides, OCS has also considered the short term and subchronic toxicity studies in the rat with halauxifen-methyl together with in vivo MOA studies in the rat to assist in identifying the most appropriate study for setting an ADI.

The short term and subchronic toxicity studies in the rat with halauxifen-methyl demonstrate a threshold for liver toxicity at 10 mg/kg bw/d, which OCS notes is below the LOAEL of 18.5 mg/kg bw/d in rabbit dams and is considered protective of maternal liver toxicity effects observed in rabbits following short-term exposure in the developmental study (noting both halauxifen-methyl and halauxifen acid were not developmental toxicants in rabbits or rats), with a LOAEL of ~50 mg/kg bw/d identified in 28 and 90–day studies in rats for AhR mediated liver toxicity. Additionally, the in vivo and in vitro MOA toxicological data demonstrated halauxifen-methyl to be a weak AhR agonist in rodents, with no evidence of sustained activation of AhR pathway in mice or rats and a reversibility of the key events for AhR mediated liver effects following pre-systemic exposure to halauxifen-methyl. Although the human relevance of an AhR-mediated MOA cannot be entirely excluded, the short-term and subchronic toxicological studies, short-term MOA in vivo studies, and in vitro mechanistic and PBPK data provide evidence that pre-systemic liver exposure in rodents does not result in sustained activation of the AhR signalling pathway, and humans are significantly less sensitive to activation of the AhR signalling pathway by halauxifen-methyl compared to rats. Overall, these data strongly support the presence of a threshold to the key events of AhR-mediated liver toxicity in rats that would be protective of human health following chronic exposure.

Therefore, OCS considers that the most appropriate study for establishing the ADI for halauxifen-methyl (halauxifen) is the 90–day dietary study with halauxifen-methyl in rats. Though this is a sub-chronic study, there is toxicokinetic data indicating the rapid hydrolysis of halauxifen-methyl to halauxifen acid, and higher NOAEL values were seen in rodent bioassays with halauxifen acid. Thus, the identified threshold for AhR mediated liver toxicity of 10 mg/kg bw/d in a subchronic rat study is considered to be protective of AhR-mediated liver toxicity following chronic exposure in humans, and does not require the use of an additional safety factor for using a study of short duration (i.e. not a chronic study) to set an ADI.

While the threshold for AhR mediated liver toxicity in rats is protective of the LOAEL for liver toxicity in maternal rabbits, the MoA for the observed liver effects in maternal rabbits has not been fully characterised. However, it is acknowledged that the observed maternal liver toxicity (i.e. increased liver weight and histopathological changes) is similar to that seen in rats suggesting that the observed liver toxicity may have occurred by the same MoA as seen in rats. Furthermore, as stated above, humans are significantly less sensitive to activation of the AhR signalling pathway by halauxifen-methyl compared to rats. Therefore, it is considered that the NOAEL identified in the 90–day oral study in rats for liver toxicity is highly conservative, as humans are less sensitive to this effect, and while the liver toxicity in rabbits has not been fully characterised it is not considered a significant data gap that requires an additional safety factor be applied.

The ADI is therefore established at 0.1 mg/kg bw/d using the NOAEL of 10 mg/kg bw/d for increased Cyp1a1 gene expression and associated increased liver weights and cholesterol (females) and increased hepatocellular vacuolation (males) observed at 53.4/52.3 mg/kg bw/d (males/females) from a 90 day dietary

study in rats and applying a 100 fold safety factor, consisting of a 10–fold safety factor for both intra- and inter-species variation.

ARfD

The acute reference dose (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.

An ARfD has not established for halauxifen-methyl based on the low acute toxicity profile of both halauxifen-methyl (pre-systemic exposure) and the major metabolite halauxifen acid (systemic exposure) in addition to the absence of acute effects in developmental, reproductive and genotoxicity studies. Halauxifen acid was not neurotoxic following acute and repeat dosing in rats, and there was also no evidence of immunotoxicity.

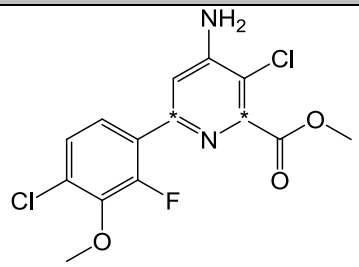
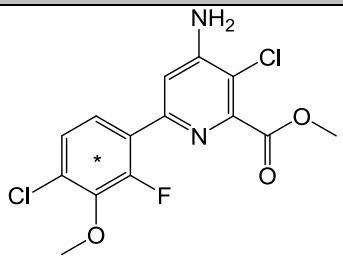
The OCS considers that pre-systemic exposure to halauxifen-methyl and systemic exposure to halauxifen acid are unlikely to present an acute hazard to humans after single dose administration.

4 RESIDUES ASSESSMENT

GF-2685 Herbicide is a water-dispersible granule formulation containing the new active constituent halauxifen-methyl together with the existing active constituent cloquintocet-mexyl. This product is intended for control of broadleaf weeds in wheat and barley. As part of the residues assessment for halauxifen-methyl, plant and animal metabolism studies, supervised residue trials, processing studies, and trade aspects were considered.

4.1 Metabolism

Metabolism data for ^{14}C-labelled halauxifen-methyl in wheat, turnips, rotational crops (lettuce, wheat and radish), rats, lactating goats and laying hens were provided.

Component	Chemical name	Structure	
Parent	Methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylate	 ^{14}C-Pyridyl-halauxifen-methyl	 ^{14}C-Phenyl-halauxifen-methyl

In the plant metabolism studies, halauxifen-methyl was applied at 10 g ai/ha (the proposed GAP), using either the pyridyl or phenyl labelled compounds. Plant matrices (wheat forage, hay, grain and straw and turnip roots and leaves) were collected at appropriate intervals. Key metabolic pathways in wheat and turnips include:

- Hydrolysis of the ester methyl group to yield halauxifen acid (XDE 729 acid);
- Hydrolysis of the methoxy group to yield methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylate (X11406790);
- Both of the above two steps can occur sequentially to yield 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid (X11449757);
- Dechlorination of the pyridine ring to yield methyl 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylate (X11861662): only observed in wheat, this is thought to result from photodegradation;
- Conjugation of X11406790 with glucose and malonic acid; and
- Incorporation of the molecule in natural products such as pectin and lignin.

The residues in the edible matrices from the metabolism studies (wheat grain and turnip roots) were not characterised, as the total radioactive residues were <0.01 mg eq./kg in all samples.

In the field residue studies for wheat, barley and oats, neither halauxifen-methyl nor halauxifen acid were generally detected in grain, while residues of halauxifen-methyl in forage and straw were much higher than those of halauxifen acid.

In the rotational crop study, after treatment of bare soil with 10 g ai/ha halauxifen-methyl (1× the proposed label rate), total radioactive residues in all crop matrices at all intervals were <0.01 mg eq./kg. Residues are not expected to be found in rotational crops.

A residue definition of parent only is proposed for halauxifen-methyl in plant commodities, for compliance with MRLs and for dietary risk assessment purposes.

In the lactating goat and laying hen metabolism studies, halauxifen-methyl was dosed at target levels of 10 ppm in feed daily for 5 days (goats) or 7 days (hens). Milk and eggs were collected during the dosing phases, with muscle, fat, hen skin and fat, liver and goat kidney being collected at sacrifice.

The key reactions occurring in the metabolism of halauxifen-methyl in rats, lactating goats and laying hens are:

- Hydrolysis of the methyl ester to yield halauxifen acid;
- Hydrolysis of the methoxy group to yield methyl 4-amino-2-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylate (X11406790);
- Both of the above two steps generally take place sequentially to give 4-amino-2-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylic acid (X11449757);
- Sulfate conjugation of X11449757 and X11406790; and
- Glucuronic acid conjugation of parent and X11406790.

The metabolite X11449757 was the only quantifiable residue in milk and tissue samples in the lactating cattle feeding study, and was the most significant residue component in the lactating goat and laying hen metabolism studies. Parent compound was barely detected at all in the metabolism studies.

A residue definition of 4-amino-2-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid, expressed as halauxifen-methyl is proposed for halauxifen-methyl in animal commodities, for compliance with MRLs and for dietary risk assessment purposes.

Analytical methods

Determination of halauxifen-methyl residues in plant commodities

Samples were extracted with acetonitrile/water, then concentrated and cleaned up using off-line or online solid phase extraction. Stable isotope internal standards ($^{13}C_6$-phenyl-halauxifen-methyl and $^{13}C_6$-phenyl-halauxifen acid) were added, followed by concentration and analysis by LC-MS/MS. The method LOQ was 0.01 mg/kg for each analyte. The methods were validated in range of matrices, including high water content (turnip root and wheat forage), dry crops (cereal grains, hay and straw), oily matrices (canola and soybean seed), acidic matrices (orange and apple), and processed wheat products (e.g. bran, flour etc), and showed good recoveries (within the generally accepted range of 70–120%) at 0.01 and 1.0 mg/kg fortification levels. The extraction efficiency of the method was validated using samples from the wheat metabolism study containing incurred residues of halauxifen-methyl, gving similar extraction efficiencies to the techniques used in the metabolism study.

Determination of cloquintocet-mexyl residues in plant commodities

An LC-MS/MS method was developed and validated for determination of cloquintocet-mexyl and cloquintocet acid in wheat matrices. Samples of wheat forage, hay, grain and straw are extracted using acetone/citrate buffer, then purified using solid phase extraction. Internal standards ($^{13}C_5$-cloquintocet-mexyl and $^{13}C_5$- cloquintocet acid) are added to the cleaned up extract before analysis by LC-MS/MS. Recoveries at fortification levels ranging from 0.005 to 0.10 mg/kg were acceptable (within the range 70–120%).

Determination of residues of halauxifen-methyl in animal tissues

Methods for determination of halauxifen-methyl and halauxifen acid in bovine and poultry muscle, liver, and fat, and eggs and milk were developed. Samples were extracted using acetonitrile/water, then cleaned up by partition with hexane. An aliquot of the acetonitrile/water phase was concentrated and further cleaned up by off-line solid phase extraction. Stable isotope internal standards ($^{13}C_6$-phenyl-halauxifen-methyl and $^{13}C_6$- phenyl-halauxifen acid) were added, followed by concentration and analysis by LC-MS/MS. The method LOQ was 0.01 mg/kg for each analyte. Acceptable recoveries (70–120%) were achieved at 0.01 and 1.0 mg/kg fortification levels in all matrices. The extraction efficiency of the method was validated using samples from the goat and hen metabolism studies containing incurred residues of halauxifen-methyl, gving similar extraction efficiencies to the techniques used in the metabolism study.

As part of the lactating cattle feeding study, the method was additionally validated for determination of the metabolite X11449757 (4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid, or desmethyl halauxifen acid), and acceptable recoveries at fortification levels of 0.01 and 0.1 mg/kg were achieved.

The methods are suitable for the proposed purposes and are acceptable.

Residue definition

The following residue definition is recommended for halauxifen-methyl for the purposes of dietary exposure assessment and for enforcement and monitoring:

Compound	Residue definition
Halauxifen-methyl	*For commodities of plant origin:* Halauxifen-methyl *For commodities of animal origin:* 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid, expressed as halauxifen-methyl

Storage stability

Storage stability data submitted with the application indicate that residues of halauxifen-methyl and halauxifen acid are stable at approximately -18 °C for at least 489 days (16 months) in wheat grain, lettuce, rapeseed, and whole oranges. Stability data for aminopyralid in wheat forage, hay, grain and straw was available to APVMA and showed that residues were stable for at least 17 months at -20 °C.

Samples of cereal grain, straw, hay and forage, rape, kale, swede and turnip forage, and swede and turnip root were analysed for halauxifen-methyl within 12 months of collection. The samples are therefore unlikely to have been adversely affected by storage.

4.2 Residue trials

Cereals

The proposed GAP for halauxifen-methyl in wheat and barley is a single 10 g ai/ha foliar application between BBCH stages 13 and 39 (3-leaf and flag leaf full emergence), with a harvest withholding period not required when used as directed, and a 14–day grazing withholding period.

A large package of residue trials conducted in Australia, New Zealand, Canada and the USA for wheat, barley and oats was supplied. Some of these included testing of cloquintocet-mexyl residues.

The combined residue dataset for halauxifen-methyl in wheat, barley and oats after application at the proposed GAP in the combined dataset were: <0.003 (20) and <0.01 (45) mg/kg.

An MRL of *0.01 mg/kg is proposed for halauxifen-methyl in cereals, with a harvest withholding period not required.

The combined dataset for halauxifen-methyl in wheat, barley and oat straw after treatment at the proposed GAP is <0.003 (20), <0.01 (42), 0.01 (2) and 0.013 mg/kg.

An MRL of 0.02 mg/kg is proposed for halauxifen-methyl in straw and fodder of cereal grains (dry), taking into account that no residues were detected in straw from the Australian trials conducted at GAP.

The combined dataset for halauxifen-methyl in wheat, barley and oat forage 2 weeks after treatment at the proposed GAP is <0.003 (11), <0.01 (4), 0.01, 0.03 (4), 0.05, 0.08 (2), and 0.10 mg/kg (dry weight).

An MRL of 0.2 mg/kg is proposed for halauxifen-methyl in forage of cereal grains (green), in conjunction with a 14–day grazing withholding period.

The proposed GAP for cloquintocet-mexyl (in GF-2685 Herbicide) is a single 10 g ai/ha foliar application between BBCH stages 13 and 39 (3–leaf and flag leaf full emergence), with a harvest withholding period not required when used as directed, and a 14–day grazing withholding period.

The combined dataset for residues of cloquintocet-mexyl in wheat, barley and oat grain is <0.003 (8) and <0.024 (35) mg/kg. The existing MRLs of *0.1 mg/kg for cloquintocet-mexyl in wheat and barley remain appropriate.

The combined dataset for cloquintocet-mexyl in wheat, barley and oat straw is <0.003 (6), 0.011, 0.015, <0.024 (34), and 0.042 mg/kg. The existing MRL of *0.1 mg/kg for cloquintocet-mexyl in straw and fodder (dry) of cereal grains [except rice] remains appropriate.

The combined dataset for cloquintocet-mexyl in wheat, barley and oat forage is <0.003 (5), 0.005, 0.01, <0.024 (3), 0.026, and 0.049 mg/kg (fresh weight). The existing MRL of *0.1 mg/kg for cloquintocet-mexyl in cereal forage (fresh weight) remains appropriate.

Cereal processing

In a processing study for wheat, grain from an untreated control plot and a plot treated at 5× the proposed GAP was process into aspirated grain fraction, bran, total bran, flour (dry mill), whole meal flour, flour-550, bread (white), whole grain bread, middlings, shorts, germ, gluten, gluten feed meal, and starch using simulated commercial processes. Residues of halauxifen-methyl and halauxifen acid were below the limit of detection in wheat grain treated at either 1× or 5× the proposed GAP, as well as in all processed commodities from grain treated at 5× the proposed rate. Separate MRLs are therefore not required for processed wheat or barley commodities.

4.3 Crop rotation

A confined crop rotation metabolism study for halauxifen-methyl showed that after a 10 g ai/ha application, which is the same as the proposed GAP for cereals and forage brassicas, total residues of halauxifen-methyl were below 0.01 mg eq./kg in all fractions of lettuce, radish and wheat at all the plantback intervals tested. Residues of halauxifen-methyl are therefore very unlikely to be detected in crops planted in rotation with a treated cereal or forage brassica crop. Residues related plantback intervals are not required for halauxifen-methyl.

Considering the application rates, the risk of residues of cloquintocet-mexyl in following crops is the same or lower than for currently registered products.

4.4 Animal commodity MRLs

A feeding study was provided for lactating cattle, while the hen metabolism study was considered for determination of likely residues in poultry commodities. In the cattle feeding study, animals were orally dosed with halauxifen-methyl daily for 28–29 days at target levels of 1, 3 and 15 ppm in feed. Milk was sampled daily, with some samples being separated into skim milk and cream for analysis. Muscle, fat, liver and kidney were collected at sacrifice, which occurred shortly after the final dose for most animals, with the remainder being maintained on untreated feed for a further 3, 5, 10 or 15 days after cessation of dosing and prior to sacrifice in order to generate depuration data.

Mammalian livestock

The calculated maximum feeding levels for halauxifen-methyl in beef and dairy cattle are 0.37 and 0.17 ppm in feed respectively.

In the lactating cattle feeding study, no residues of parent compound, or the metabolites halauxifen acid (XDE-729 acid), or X11449757 were found above the LOQ (0.01 mg/kg) in milk at any of the feed levels (1.06, 3.16, or 15.31 ppm), while a few low level detections below the LOQ were made, nearly all of X11449757 in milk from the high dose group.

An MRL of *0.01 mg/kg is therefore proposed for halauxifen-methyl in milk.

No residues of halauxifen-methyl parent were detected in muscle, fat, liver or kidney at any of the feed levels. A few low level detections (<LOQ) of XDE-729 acid were made in kidney only for the low and high dose groups. X11449757 was not detected in fat samples for the low or mid dose groups, while being found at up to 0.012 and 0.014 mg/kg in mesenteric and perirenal fat respectively for the high dose group (residues expressed as parent equivalents). In liver, maximum levels of 0.012, 0.045, and 0.216 mg/kg were observed for the low, mid and high dose groups respectively, while for kidney, the maxima were 0.005 (<0.01), 0.022, and 0.066 mg/kg respectively (residues expressed as parent equivalents).

Given that neither parent compound nor the metabolites were detected in muscle or fat after feeding at 1.06 ppm, which is approximately 2.86× the calculated maximum feeding level for beef cattle, residues of halauxifen-methyl or its metabolites are not expected to be detected in meat or fat of livestock consuming treated feed. An MRL of *0.01 mg/kg is therefore proposed for meat (mammalian).

Scaling the residues of X11449757 observed in liver and kidney after feeding at 1.06 ppm for the calculated maximum feeding level of 0.37 ppm gives expected residues of X11449757 (the residue definition for animal commodities) of 0.0042 and 0.0017 mg/kg respectively. As the calculated residue level in liver is above the limit of detection (but below the LOQ), an MRL of 0.01 mg/kg is recommended for halauxifen-methyl in edible offal (mammalian). The depuration phase of the feeding study showed that residues clear rapidly from liver and kidney, with a half life of ≤1 day.

Poultry

The only significant poultry feeds that may contain residues of halauxifen-methyl are cereal grains and their byproducts such as bran and milling waste. Given that detectable residues of halauxifen-methyl are not expected to be found in cereal grains, residues of cereal grain in poultry feed will be effectively nil. MRLs at the LOQ (*0.01 mg/kg) are recommended for poultry meat, poultry edible offal, and eggs.

4.5 Spray drift

At the low dose in the halauxifen-methyl feeding study (1.06 ppm), the only tissue for which quantifiable residues were observed was liver, at 0.012 mg/kg parent equivalents. Scaling this result for the LOQ, and proposed MRL for mammalian edible offal of 0.01 mg/kg gives a maximum level of 0.88 ppm for feeding to ensure no quantifiable residues of halauxifen-methyl or its metabolites.

Application by both ground and aerial methods is proposed on the product labels. The labels also specify coarse droplet size. Using the ground application spreadsheet for coarse droplet high boom broadacre application in the APVMA Standard Spray Drift Risk Assessment Scenarios and assuming a minimum pasture density of 1500 kg dry matter per hectare shows that even at a distance of 2 metres from the edge of the application area, the concentration of halauxifen-methyl in pasture subject to downwind drift will only be 0.48 mg/kg. Therefore, no spray drift mitigation measures are required for ground application of halauxifen-methyl in order to ensure that residues in animal commodities are below the LOQ.

Using the standard spray drift assessment spreadsheets for a 20 km/h wind, coarse droplet size, and a pasture density of 1500 kg dry matter per hectare, and taking the average over a 300 metre distance downwind

(a typical paddock size) gives a mean pasture concentration of 0.28 mg/kg for planes and 0.32 mg/kg for helicopters. These are both well below the calculated feeding level above, and hence no spray drift mitigation measures are required for aerial application of halauxifen-methyl in order to ensure that residues in animal commodities are below the LOQ.

At the proposed application rates the spray drift risk of cloquintocet-mexyl on to adjacent crops or pasture following use of GF-2685 Herbicide is considered acceptable.

4.6 Bioaccumulation potential

The octanol-water partition coefficient ($log_{10}K_{OW}$ value) for halauxifen-methyl is 3.75, 3.76, and 3.92 at pH values of 5, 7, and 9 respectively, at 20 °C. No data were provided for XDE-792 acid, or X11449757. However, these compounds are expected to be more water soluble and have lower $log_{10}K_{OW}$ values than the parent.

In the lactating cattle feeding study, low level quantifiable residues were observed in mesenteric and perirenal fat at the highest feeding level, while parent and the two metabolites were not detected in muscle. This and the $log_{10}K_{OW}$ value indicates some tendency for fat solubility and potential for bioaccumulation. However, given that the main residue component in animal tissues is expected to be the metabolite X11449757, which is expected to be less fat soluble than parent compound, and since quantifiable residues are not expected to be found in mammalian or poultry meat, it is not proposed to establish MRLs with an 'in the fat' designation.

4.7 Risk Assessment Conclusions

Estimated dietary intake

The chronic dietary intake risk for halauxifen-methyl has been assessed. The ADI for halauxifen-methyl is 0.1 mg/kg bw/day, based upon a NOEL of 10 mg/kg bw/day and a 100–fold safety factor. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for halauxifen-methyl, is equivalent to <1% of the ADI. DIAMOND Modelling[3] of chronic dietary exposure is also performed on new chemicals. The DIAMOND model estimated the chronic dietary exposure of halauxifen-methyl as <1% of the ADI for the general population.

An acute reference dose (ARfD) has not been established for halauxifen-methyl due to the lack of an identified acute toxicological hazard.

It is concluded that the dietary exposure to halauxifen-methyl is low and the risk from residues in food is acceptable when GF-2685 Herbicide is used according to label directions.

No changes are required for Table 1 MRLs for cloquintocet-mexyl, or the tank mix product actives MCPA or clopyralid are required, and no changes to the dietary risk is expected for these actives.

[2] Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.
[3]. DIAMOND: The Diamond Modelling of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ.

Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of GF-2685 Herbicide:

Table 1

COMPOUND		FOOD	MRL (MG/KG)
ADD:			
Halauxifen-methyl			
GC	0080	Cereal grains	*0.01
MO	0105	Edible offal (mammalian)	0.01
PE	0112	Eggs	*0.01
MM	0095	Meat (mammalian)	*0.01
ML	0106	Milks	*0.01
PO	0111	Poultry, edible offal of	*0.01
PM	0110	Poultry meat	*0.01

Table 3

COMPOUND	RESIDUE
ADD:	
Halauxifen-methyl	*Commodities of plant origin:* Halauxifen-methyl *Commodities of animal origin:* 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid, expressed as halauxifen-methyl

Table 4

COMPOUND		ANIMAL FEED COMMODITY	MRL (MG/KG)
ADD:			
Halauxifen-methyl			
		Forage brassicas (green)	1
AF	0081	Forage of cereal grains (green)	0.2
AS	0081	Straw and fodder of cereal grains (dry)	0.02

The following withholding periods are required in conjunction with the above MRLs:

HARVEST WITHHOLDING PERIODS:

Cereals	Not required when used as directed.

GRAZING WITHHOLDING PERIODS:

Cereals	14 days
Forage brassicas	14 days

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported and main destinations

Wheat, barley, oat hay, and meat and dairy products are major export commodities.

Finite residues are not expected to be found in wheat, barley or triticale, and an MRL of *0.01 mg/kg is proposed for halauxifen-methyl in cereal grains.

The total exports of Australian barley were 5165 kilotonnes in 2012/13, valued at $1.626 billion[4]. Key export markets for barley are China, Saudi Arabia, Japan, Korea, Thailand, Vietnam, the Philippines, Kuwait, and Taiwan. The total exports of Australian wheat (including flour) were 21265 kilotonnes in 2012/13, valued at $6.776 billion. Key export markets for wheat are Indonesia, Iraq, Korea, Iran, Vietnam, China, Japan, the Philippines, Malaysia, and Yemen.

Finite residues may be found in oat hay. An MRL of 0.2 mg/kg is proposed for forage of cereal grains (green).

Approximately 720 kilotonne of hay is exported from Australia, to the value of ~$230–250 million, per annum[5]. Approximately 85% of exports are oaten hay, while 10% is straw and the balance is predominantly lucerne hay and chaff. Approximately 85% of Australian export hay is destined for Japan, while the volume of hay exported to China and the UAE is increasing.

MRLs of *0.01 mg/kg are proposed for halauxifen-methyl in mammalian meat and milk, poultry meat, poultry edible offal and eggs. Trace residues may be observed in mammalian edible offal but are not expected to exceed 0.01 mg/kg. An MRL of 0.01 mg/kg is proposed. The depuration phase of the cattle feeding study showed that residues clear rapidly from liver and kidney, with a half life of ≤ 1 day.

The significant export markets for animal commodities are listed in Part 5B of Residues Guideline[6]. Total exports of dairy products in 2012/13 were worth $2.17 billion, with key export destinations including Japan, Singapore, China, Indonesia, Malaysia, Thailand, the Philippines, Korea, Russia, and the USA. MRLs for halauxifen-methyl in animal commodities are not currently established or proposed in overseas markets.

5.2 Overseas registration status

The residues aspects of halauxifen-methyl have not been considered by the Joint Meeting on Pesticide Residues (JMPR).

[4] Agricultural Commodity Statistics 2013, Australian Bureau of Agricultural and Resource Economics and Sciences
[5] Personal communication, AFIA, August 2010
[6] http://www.apvma.gov.au/morag_ag/vol_3/part_05b_trade.php

The following relevant Australian and overseas MRLs for plant commodities have been established or proposed:

Halauxifen-methyl plant commodity MRLs

Country	*Residue definition*	*Commodity*	*MRL (mg/kg)*
Australia (proposed)	Halauxifen-methyl	Cereal grains	*0.01
		Forage of cereal grains (green)	0.2
		Straw and fodder of cereal grains (dry)	0.02
Canada (proposed)	Halauxifen-methyl	Barley	*0.01
		Wheat	*0.01
USA (proposed)	Halauxifen-methyl	Barley grain	0.01
		Barley hay	0.01
		Barley straw	0.01
		Wheat forage	0.5
		Wheat grain	0.01
		Wheat hay	0.04
		Wheat straw	0.015

The following Australian animal commodity MRLs/tolerances have been proposed:

Halauxifen-methyl animal commodity MRLs

COUNTRY	RESIDUE DEFINITION	COMMODITY	MRL (MG/KG)
Australia (proposed)	4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid, expressed as halauxifen-methyl	Edible offal (mammalian)	0.01
		Eggs	*0.01
		Meat (mammalian)	*0.01
		Milks	*0.01
		Poultry, edible offal of	*0.01
		Poultry meat	*0.01

Although at this stage, the USA and Canada have not proposed any animal commodity MRLs for halauxifen-methyl, the USA and Canada have agreed to harmonise with Australia on a residue definition of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid, expressed as halauxifen-methyl for animal commodities.

5.3 Potential Risk to Trade

The risk to trade in cereal grains and animal commodities is expected to be low, as finite residues of halauxifen-methyl are not expected to be found in cereals, mammalian or poultry meat or offal, eggs, or milk. Finite residues of halauxifen-methyl may be found in oaten hay, however it is noted that the Japan does not have a maximum level for halauxifen-methyl in animal feeds, and the risk to exports of oaten hay to Japan is expected to be low[7].

No changes are proposed to MRLs for cloquintocet-mexyl. In any case, MRLs for cloquintocet-mexyl in cereal grains, forage, and fodder and animal commodities are established at the LOQ. Therefore, residues of cloquintocet-mexyl resulting from the proposed use of *GF-2685 Herbicide* will not change the already low risk to trade.

[7] Regulatory Frameworks to Ensure Feeds Safety in Japan, Food and Agricultural Materials Inspection Center, www.famic.go.jp/ffis/feed/r_safety/r_feeds_safety.html

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Halauxifen-methyl (CAS: 943831-98-9) is not listed on Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2014).

The active constituent cloquintocet-mexyl (CAS: 99607-70-2) is listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2014) with the following risk phrases:

R43	May cause sensitisation by skin contact

The following cut-offs apply for the active constituent:

Conc. ≥ 1%	Xi; R43

Based on the concentration of cloquintocet-mexyl in the product and according to the NOHSC cut-off listed on the Safe Work Australia (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2014), the formulated product should have risk phrase 'R43: May cause sensitisation by skin contact'.

6.1 Formulation, packaging, transport, storage and retailing

The active constituent halauxifen-methyl will be manufactured overseas. The product GF-2685 Herbicide will be manufactured overseas and imported into Australia in HDPE bottles/jerry cans 1, 5 and 10 kg in size and in 0.5, 1 and 5 kg foil satchels.

6.2 Use pattern

The product GF-2685 Herbicide containing 100 g/kg halauxifen (as halauxifen methyl ester) and 100 g/kg cloquintocet-mexyl in a WG formulation, is intended for post-emergent control of hard to kill broad leaf weeds in wheat and barley.

The product is intended for occupational use only by commercial applicators and farmers. The applicant has indicated that spray application to wheat and barley crops (winter crops) is only required once in the growing season during spring at the post-emergent stage BBCH 39 (flag leaf fully emerged on main stem with ligule showing). Based on the use pattern of the product exposure is likely to occur via the dermal and inhalational route during mixing/loading and application with ocular exposure also possible. The duration of exposure is expected to be short-term in duration.

The product will be tank mixed with uptake spraying oil at a dilution rate of 50 mL/100 L (1 in 2000 dilution). Toxicological implications for such combination treatments have not been assessed by OCS in this application. Application is intended as a dilute spray in 50–100 L of water via aerial or ground boom application at a maximum rate of 100 g product per hectare (equivalent to 10 g/ai ha halauxifen and cloquintocet-mexyl).

6.3 Exposure during use

Commercial applicators and farmers are the intended users of the product. It is not intended for use in the domestic market. Workers may be exposed to the product when opening containers, mixing/loading, application and cleaning up spills and equipment. The main route of exposure to the product and diluted spray will be dermal and inhalational, although ocular exposure is also possible.

From comparison of the NOAEL/NOELs from the toxicological data available for halauxifen-methyl and cloquintocet mexyl, and suitable for occupational risk assessment of dermal and inhalation exposure, and consideration of relevant absorption factors, MOEs and concentrations of the active constituents in the product (equivalent concentrations) it was considered that occupational exposure to cloquintocet-mexyl in the product will be the driving force of toxicity.

Therefore, the NOAEL/NOELs for occupational risk assessment of dermal and inhalational exposure are 200 mg/kg bw/d and 1.22 mg/kg bw/d to be compared against an MOE of 100. No dermal absorption factor is required as the dermal NOEL is derived from a study using the appropriate route of exposure and in the absence of data a default value of 100% has been assumed for inhalation absorption.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate potential worker exposure.

The MOE's for the workers associated with short-term repeat use of the product when mixing and loading, application by groundboom (open cab) and aerial application methods without any recommended protective clothing or engineering controlsare acceptable (i.e. >100).

The acute hazards of concern associated with the product are slight skin and eye irritation and skin sensitisation.

6.4 Exposure during re-entry

Workers may be exposed to GF-2865 Herbicide when re-entering treated crop areas. In the absence of worker exposure studies, the post-application exposure has been calculated using the Occupational Post-Application Risk Assessment Calculator Version 1 (8/9/00) EPA Policy 003.1.

Based on MOEs much greater than the acceptable level (100) on day 0 post-application for high exposure activities in barley and wheat crops there is no re-entry risk associated with this product and a nil re-entry statement has been recommended.

6.5 Recommendations for safe use

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

6.6 Conclusion

The registration of GF-2685 Herbicide containing 100 g/L halauxifen (as methyl ester) and 100 g/L cloquintocet mexyl for the control of broadleaf weeds in barley and wheat crops is supported.

GF-2685 Herbicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Material Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

Dow AgroSciences Australia Limited has applied for registration of a 100 g/kg WG formulation (GF-2685). The product contains two active constituents. Halauxifen-methyl is a new active constituent, which has been assessed as part of a global joint review (GJR). The second active constituent, cloquitocet-mexyl, has previously been assessed by the Department of the Environment. Halauxifen-methyl is a member of the pyridine carboxylic acid family. Cloquintocet-mexyl is a crop safener substance. It is a quinoline-derivative.

The proposed use in Australia is for post-emergent control of broadleaf weeds in wheat and barley.

The environmental fate and ecotoxicity information following in the PRS relate to the new active constituent, halauxifen-methyl, or for test results relating to the end-use product.

7.1 Environmental Fate

Hydrolysis

Halauxifen-methyl is expected to be relatively hydrolytically stable under normal environmental conditions except under mildly basic conditions. At 25^{o}C, the calculated half-lives were 80.9, 155 and 3.04 days at pH 4, 7 and 9 respectively.

Photolysis/Photodegradation

Aqueous photolysis may provide an important removal route for halauxifen-methyl in the environment with phototransformation and environmental half-lives being <10 minutes (pH 7, 40^{o}N latitude).

Biodegradation

Soil Metabolism

Degradation of the parent compound in aerobic soils tends to follow a bi-phasic pattern with faster initial degradation. The range of DT50s for the parent compound indicated shorter persistence under laboratory conditions than those found in the field. Laboratory aerobic soil half-lives at 20^{o}C ranged from 1.08 days to 2.13 days (4 soils). In the same soils, but under sterile conditions, half-lives ranged from 7.45 days to 9.75 days. Degradation was still rapid in these soils in laboratory tests under anaerobic conditions with half-lives ranging from <1 day to 2.75 days.

Field dissipation results were available for 6 different sites in North America and four different sites in Europe. In the European studies, the same sites were utilised to consider dissipation under autumn or spring conditions. The maximum field half-life was 37.9 days (UK soil in spring). However, all other half-lives were <20 days with a range of 1.54 days to 17.6 days.

Of the major metabolites considered, the shortest half-lives, based on laboratory degradation data, were associated with the acid (XDE-729 Acid) with aerobic soil half-lives of 3.5–19.5 days. The phenolic acid X11449757 had aerobic laboratory soil half-lives of 19.5–70 days. The field half-life results for the main acid

metabolite have been calculated from peak residues in some of the field trials, and these again show the substance can be more persistent in the field than in laboratory experiments with half-lives potentially >100 days.

Aquatic metabolism

Where it is exposed to aerobic water/sediment systems, the half-life in the water column is expected to be short (up to a few days). Initial transformation to either XDE-729 Acid or the phenol X11406790 was relatively fast with peak concentrations found within 2–8 days. As these metabolites were further degraded to X11449757, this metabolite was found at high peak concentrations relative to the parent compound.

In a sandy loam system, in terms of total amount of X11449757, it reached a maximum ~75% of parent on day 22 (48.3% in water; 27.3% in sediment). Water concentrations declined after this while sediment concentrations peaked at 35.4% at day 62. In this system, the calculated half-life of X11449757 was 37.7 days based on a single first order kinetic model while half-lives for the acid and X11406790 were 11.6 days and 6.7 days respectively (single first order). In a silt loam system, a similar pattern was observed. The half-life for the acid and X11406790 were faster at 2.96 days and 2.19 days respectively (single first order). However, the whole system half-life for X11449757 was slower at 81.6 days (single first order). The half-life in water was calculated to be around 20 days.

Similar rapid removal of halauxifen-methyl was found in an anaerobic water/sediment study in two separate systems. Again, initial transformation to either XDE-729 Acid or X11406790 was fast with peak levels after 1– 3 days. These were further degraded to X11449757 with apparent full conversion to this metabolite (97.2– 100.6% of initially applied). The half-life of halauxifen-methyl in the water column was <1 day. In terms of the whole system, degradation of halauxifen-methyl was 1 day or less, while the acid metabolite and X1140690 were degraded with whole system half-lives of 6 or less days.

Mobility

In standard batch adsorption tests, halauxifen-methyl was tested in six different soils with %OC ranging from 1.1–4.4%. Koc values ranged from 378–2453 L/kg. In five of these soils, halauxifen methyl can be considered to have at least low mobility (Koc 500–2000 L/kg) while it has medium mobility in the sixth soil (Koc 150– 500 L/kg). The Kdes following the first desorption step was higher than the Kads, indicating that adsorption is not fully reversible.

XDE-729 Acid, which can be formed at high levels relative to the parent compound, was tested in the same six soils and showed Koc values of 28–178 L/kg. This metabolite is classed as having very high mobility in two soils (Koc 0–50 L/kg) and generally has high mobility (Koc 50–150 L/kg). Similar results were found for the secondary soil metabolite, X11449757.

In field studies, there was limited movement of halauxifen-methyl or its main metabolites through the soil profile with generally limited findings below 20 cm found in two European studies. In US field dissipation studies halauxifen-methyl and/or its metabolites were found at deeper levels in isolated cases.

Bioaccumulation

Halauxifen-methyl is not expected to bioconcentrate in organisms and was shown to be rapidly depurated from fish following exposure.

7.2 Environmental Effects

Avian

Halauxifen methyl is practically nontoxic to birds with acute oral or short term dietary exposure (acute oral LD50 > 2250 mg ac/kg bw for both bobwhite quail and zebra finch; 5 d dietary LC50 > 6000 ppm for both bobwhite quail and mallard duck). Reproduction studies indicated NOECs of 403 ppm and 1040 ppm for bobwhite quail and mallard duck, respectively.

Fish

Based on the results of acute toxicity studies conducted with the active constituent, halauxifen-methyl is categorised as moderately toxic to fish. The 96 h LC50 to rainbow trout was calculated to be 2.01 mg ac/L while for fathead minnow and sheepshead minnow, there was <50% mortality at the highest test concentrations of 3.22 mg ac/L and 1.33 mg ac/L respectively (approaching maximum solubility under the test conditions). Acute toxicity testing with tadpoles indicates halauxifen-methyl is at worst, moderately toxic to these organisms with a 96 h LC50 >2.0 mg/L.

Early life stage toxicity studies with halauxifen-methyl indicated a 35 d NOEC of 0.259 mg ac/L to fathead minnow, and a 36 d NOEC of 0.0115 mg ac/L (LOEC = 22.9 mg ac/L, effects on fry survival) to sheepshead minnow. Thus halauxifen-methyl can be classified as moderately toxic to fish with chronic exposure.

In short term reproduction studies there did not appear to be any treatment related impacts on endocrine end-points assessed for either the parent compound or acid metabolite. There was an apparent effect on fecundity in fish from the parent compound, however, the fertility of the eggs produced did not appear to be impacted. Based on the Australian use pattern, exposure levels of 77 μg/L (the lowest level tested) in the environment and for extended times (21 d in this test) are not expected.

The metabolites XDE-729 Acid, X11449757 and X11406790 were tested for acute toxicity to rainbow trout. XDE-729 Acid and X11449757 were practically non-toxic (LC50's >100 mg/L) while X11406790 can be considered at worst, slightly toxic with an LC50 >29 mg ac/L. XDE-729 Acid and X11449757 were tested in early life stage testing with fathead minnow and were both were very slightly toxic with NOECs >10 mg/L and 8.9 mg/L respectively.

Aquatic Invertebrates

Based on the results of acute toxicity studies conducted with the active constituent, halauxifen-methyl is classified as moderately toxic (EC50 = 2.12 mg ac/L). Acute testing with the mysid shrimp and eastern oyster did not result in 50% mortality or effects at the highest tested rates of 1.3 mg/L and 1.21 mg/L, respectively.

A 21 day chronic toxicity study of halauxifen-methyl to *Daphnia magna* indicated a NOEC of 0.114 mg ac/L based upon treatment-related effects on total live young. A 28 day chronic toxicity study of halauxifen-methyl to mysid shrimp indicated a NOEC of 0.152 mg ac/L (nominal concentration – P-generation growth). Thus halauxifen-methyl can be classified as slightly toxic to aquatic invertebrates with chronic exposure (NOEC 1– 0.1 mg ac/L).

The metabolites XDE-729 Acid, X11449757 and X11406790 were tested for acute toxicity to *Daphnia magna*. XDE-729 Acid and X11449757 were practically non-toxic (LC50's >100 mg/L) while X11406790 can be considered at worst, slightly toxic with an LC50 >25 mg ac/L. XDE-729 Acid was tested in a 21 d reproduction study with Daphnia magna and was practically non-toxic with a NOEC of 98.3 mg/L.

10 day whole sediment tests were undertaken with midge larvae (*Chironomus dilutus*) and the marine amphipod (*Leptocheirus plumulosus*) with exposure through spiked sediment. Halauxifen-methyl was, at worst, moderately toxic to these species with EC/LC50 values of >89.3 mg/kg dw sediment and >58.1 mg/kg dw sediment respectively.

A 28–day toxicity tests was conducted with *Chironomus riparius* in the presence of sediment with exposure through the water column. There were no effects on the midge at the highest tested rate of 1.26 mg ac/L.

Algae, Diatoms and Aquatic Plants

In testing with algae and aquatic plants, the test substance was unstable during the testing. Halauxifen-methyl was moderately toxic to the four standard algae species with 96 h ErC50 and EbC50 values >1 mg ac/L. Also, when tested with the standard floating aquatic macrophyte, *Lemna gibba*, halauxifen-methyl was moderately toxic with the most sensitive 7 d EC50 of 3.58 mg/L based on frond count yield. However, when tested on the rooted aquatic macrophyte, *Myriophyllum spicatum*, the active constituent was very highly toxic. The most sensitive end-point was shoot length, and the 14 d yield and growth rate EC50 values were 0.149 and 0.393 µg ac/L respectively. This is several orders of magnitude more sensitive than toxicity to *Lemna gibba*.

The sensitivity exhibited by the parent compound to this rooted aquatic macrophyte is supported by testing with the end-use product. The end-use product showed only slight toxicity based on biomass and was practically non-toxic based on growth rate to the freshwater green alga *Pseudokirchneriella subcapitata*. The most sensitive end-point for the floating macrophyte *Lemna gibba* was frond count yield with a 7 d EC50 of 35.6 mg product/L. The product proved very highly toxic to the rooted aquatic macrophyte *Myriophyllum spicatum*. Shoot length was again a sensitive end-point and the 14 d growth rate and yield EC50 values were 102 and 66.6 µg product/L respectively. The growth rate EC50 based on biomass was 84.4 µg product/L.

XDE-729 Acid was slightly toxic to the four standard algae species and the floating aquatic macrophyte *Lemna gibba* with growth and biomass EC50 values >10 mg/L. However, like the parent compound, this metabolite was very highly toxic to the rooted aquatic macrophyte *Myriophyllum spicatum*. Again, the most sensitive end-point was shoot length and the 14 day yield and growth rate EC50 values for this end-point were 0.80 and 1.58 µg/L.

Metabolite X11449757 was moderately toxic to the green algae, *Pseudokirchneriella subcapitata* based on yield and biomass, and slightly toxic based on growth rate. It was essentially practically non-toxic to the floating aquatic macrophyte *Lemna gibba*. This metabolite was tested for effects on the rooted macrophyte,

Myriophyllum spicatum but no effects were observed up to the highest tested concentration of 100 µg/L (0.1 mg/L).

Similarly, metabolite X11406790 was moderately toxic to the green algae, *Pseudokirchneriella subcapitata* based on yield and biomass, and slightly toxic based on growth rate. It was at worst, slightly toxic to the floating aquatic macrophyte *Lemna gibba*. This metabolite was tested for effects on the rooted macrophyte, *Myriophyllum spicatum* but no effects were observed up to the highest tested concentration of 100 µg/L (0.1 mg/L).

Terrestrial Invertebrates

Halauxifen-methyl was shown to not be toxic to bees, soil dwelling organisms or non-target arthropods. In the case of bees, oral and contact LD50s were >98 µg/bee and >100 µg/bee respectively.

The end-use product was tested on the standard beneficial insects, the parasitoid (*Aphidius rhopalosiphi*) and the predatory mite (*Typhlodromus pyri*) in glass plate tier 1 laboratory dose/response tests. For both species, there were no effects on mortality or reproduction with LR50's >1000 g product/ha.

Acute toxicity tests for earthworms showed halauxifen-methyl and its major metabolites to not be toxic with LC50's >1000 mg/kg dw soil in all cases. For reproductive toxicity testing, halauxifen-methyl and its major metabolites all resulted in a NOEC of 10 mg/kg soil dw, the highest rate tested.

There were no effects from halauxifen-methyl or its major metabolites on mortality of the soil predatory mite (*Hypoaspis aculeifer*) or the collembolan (*Folsomia candida*). The halauxifen-methyl acid metabolite showed slight effects on reproduction of the soil predatory mite (NOEC = 6.25 mg/kg soil) while exposure of the collembolan to X11449757 resulted in inhibition of reproduction of >10% at concentrations exceeding 0.31 mg/kg dw (up to the maximum 10 mg/kg tested).

Microorganisms

Exposure of halauxifen-methyl and its major metabolites to soil microorganisms showed no significant adverse effects on the soil nitrogen cycle or soil respiration at levels up to 0.05 mg ac/kg dw soil, the highest tested rate.

Terrestrial Plants

Testing on the Australian end-use product, GF-2685, was undertaken using standard tier II terrestrial vegetation test methods.

Plants generally appeared less susceptible when exposed through soil application (applied to the soil surface, pre-emergence) than when application was to the foliage of emerged plants. In the seedling emergence study, fresh weight measurements resulted in the more sensitive effect. The most sensitive plant was the dicot, carrot, with an ER50 of 7.47 g acid equivalent/ha and an ER25 of 4.42 g ac/ha.

In vegetative vigour testing, fresh weight was significantly affected in onion, ryegrass, soybean, cucumber, sugar beet, tomato and carrot. Height was significantly affected in onion, corn, oilseed rape, soybean,

cucumber, tomato and carrot. Survival was significantly affected in soybean, cucumber and carrot. The most sensitive plant in terms of mortality was the soybean. The LR50 calculated for soybean was 1.72 g acid equivalent/ha.

Seedling emergence tests were undertaken with halauxifen-methyl acid and X11449757. In the acid test the most sensitive monocotyledon species was onion, with an ER50 value of 10.382 g/ha. Carrot was the most sensitive dicotyledon species to pre-emergence applications of XDE-729 acid, with an ER50 value of 0.3835 g/ha. No effects were found up to 15 g/ha with X11449757.

7.3 Environmental Risk Assessment

Halauxifen-methyl is to be applied at application rates of 5 g ac/ha or 10 g ac/ha, with a single applications per crop. The risk assessment, which was performed using standard methodology, showed an acceptable risk to all environmental organisms considered.

The spray drift risk assessment was undertaken as per the APVMA spray drift policy and demonstrated risk to aquatic organisms and terrestrial plants is acceptable, provided the inclusion of appropriate downwind aquatic and terrestrial spray drift buffer zones are applied. The runoff risk assessment to aquatic organisms was undertaken as per the Department of the Environment screening model and demonstrated that risk to aquatic organisms from runoff of both active constituents, and halauxifen-methyl acid, was acceptable.

The Department of the Environment recommends that the APVMA be satisfied that the proposed use of this product is unlikely to have an unintended effect that is harmful to animals, plants or things or the environment.

8 EFFICACY AND SAFETY ASSESSMENT

The efficacy and crop safety trial data submitted to support this application comprised a large number of trials (50) conducted in most states of Australia (with the exception of Tasmania and the two territories) over 2009– 11. The major objective of this trial work was to demonstrate the efficacy of GF-2685 Herbicide in controlling a range of broadleaf weeds in wheat and barley crops, as well as demonstrating its selectivity or safety for use in those crops and finally trying to identify the critical factors related to breakdown of the herbicide in the soil so that minimum safe re-crop timelines for sensitive spp. could be established GF-2685 Herbicide showed that against weeds such as Deadnettle, Denseflower Fumitory, Sub-clover and Mexican Poppy it was very effective, with an average level of control being achieved of 95-100% in trials with rates of application of the product at 50 g/ha. Following on from these was Flaxleaf Fleabane which while not being quite as susceptible as the previous group, it was found that effective control of this weed could be achieved with rates of GF-2685 Herbicide at 50 g/ha as long as they were below a certain size and age. Bigger and older plants required increasing the rate to 100 g/ha.The next group of weeds; Rough Sowthistle, milkthistle and Prickly Lettuce were all much harder to control than the previous two groups, mostly because they belong to a family (Asteraceae) of plants which is notoriously difficult to control with herbicides which don't contain some component of `phenoxy' herbicides (e.g. MCPA). Consequently, control of these weeds to a commercially acceptable level can be found with rates of GF-2685 Herbicide at 100 g/ha, but only to plants which are not older than the 6 leaf stage of growth and not larger than 10 cm in diameter.

All GF-2685 Herbicide treatments are recommended to be applied with an adjuvant/wetter and the one most consistently used in these trials, and which is also recommended on the label is Uptake Spraying oil applied at a rate of 0.5% or 500 m1/100 L water. Selectivity, or crop safety to GF-2685 Herbicide was also explored in the trial data submitted for this application, and in an extensive series of trials (14) conducted over a number of years on wheat and barley it was seen that cultivars within those two species are quite tolerant to this herbicide. In these herbicide tolerance trials the recommended rate of GF-2685 Herbicide (100 g/ha) and either 1.5 times or twice that rate was applied to various varieties of wheat and barley to determine not only their tolerance to the herbicide but also to try and establish where the safety margin might lie given occasions of overlap and overspray.

The results showed that wheat and barley cultivars are quite tolerant of this herbicide, even when double the recommended rate is applied, and this was demonstrated through lack of visual injury as well as grain yields compared to untreated controls. Occasionally there were some outlier results which showed a possible sensitive reaction to the herbicide but this is more likely to be experimental error as the responses were not consistent with either the rate of herbicide applied or between years.

Plant back time periods for sensitive crops when planting into paddocks or areas previously treated with GF- 2685 Herbicide 85 was also explored in this submission. Working on the premise that this herbicide is mainly broken down in the soil by biological activity, these trials examined rainfall amounts and time periods in various soil types to determine what the safe re-cropping intervals may be after use of this herbicide. The responses to this work were somewhat variable and the reason for this may be related more to the quality of the rainfall than the actual volume of rain received, or even to the soil type involved. Biological activity in the soil is related to available moisture and temperature of the soil., and the greatest breakdown occurs when soil is wet and warm for lengthy periods of time. Even if a total volume of rain is received that might meet the criteria, if it comes in short sharp busts and a consistent cycle of wetting and drying then it is likely to support less biological activity, than if one or two larger events equivalent to the same volume are received in that time

period. Consequently, conservative timelines are given for re-cropping intervals which range from 100–200mm rainfall and 7 months of time for spp. such as pulses and pasture legumes. Even if these are strictly observed it would be expected that in most situations a mid-season application of GF-2685 Herbicide would not breach the re-crop interval, and it would only be a late application followed by a dry summer/autumn where some discretion on the next season's crop type would be required.

In summary, GF-2685 Herbicide is a new herbicide with a different chemical background to the majority of herbicides available to control the weeds on its label and as such represents a new opportunity to achieve effective broadleaf weed control without increasing the possible risk of herbicide resistance or tolerance development. GF-2685 Herbicide can also be effectively deployed in most rotational cropping enterprises as its residual life in the soil is relatively short making it suitable in many situations.

Therefore, in terms of the evidence of the efficacy and crop safety of the product, the application by Dow AgroSciences Australia Limited to register GF-2685 Herbicide for the control of a range of broadleaf weeds in wheat and barley crops as per the label claims is supported when used in accordance with the proposed label instructions.

9 LABELLING REQUIREMENTS

CAUTION

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

Dow AgroSciences

GF-2685

Herbicide

ACTIVE CONSTITUENT: 100 g/kg HALAUXIFEN as the methyl ester
100 g/kg CLOQUINTOCET- MEXYL

GROUP I HERBICIDE

A wettable granule formulation for post-emergent control of broadleaf weeds in wheat and barley as specified in the Directions for Use.

Dow AgroSciences Australia Limited
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20 Rodborough Road
FRENCHS FOREST NSW 2086
www.dowagrosciences.com.au
CUSTOMER SERVICE TOLL FREE: **1-800 700 096**

Contents: 500 g, 1, 5 and 10 kg

GMID:

DIRECTIONS FOR USE

RESTRAINTS

DO NOT apply to crops or weeds which may be stressed due to a range of factors including, but not limited to: drought, or water logging; prolonged or severe frosts; sustained high temperatures; poor nutrition (including deficiency and trace element toxicity); root diseases; or previous herbicide treatment as reduced weed control and / or increased crop injury may result.

DO NOT apply if rain is likely within 3 hours as weed control may be reduced.
DO NOT apply to oats.
DO NOT apply to cereals after full flag leaf emergence (BBCH 39).

SPRAY DRIFT RESTRAINTS

DO NOT apply GF-2685 with spray droplets smaller than a coarse spray droplet size category according to the 'APVMA Compliance Instructions for Mandatory COARSE or VERY COARSE Droplet Size Categories' located under this title in the **GENERAL INSTRUCTIONS** section of this label.

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 KEEP this record for a minimum of 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/situation and weed/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.)

Aquatic Areas

DO NOT apply if there are aquatic or wetland areas including aquacultural ponds downwind from the application area and within the **mandatory no-spray zones** shown in the table below.

Table 1 – No-Spray Zones for Protection of the Aquatic Environment		
FOR AERIAL APPLICATION		
Wind Speed Range at Time of Application	**Downwind Mandatory No-Spray Zone**	
	Fixed-Wing	**Helicopter**
from 3 to 8 kilometres per hour	20 metres	20 metres
from 8 to 14 kilometres per hour	20 metres	20 metres
from 14 to 20 kilometres per hour	20 metres	20 metres
FOR GROUND APPLICATION		
from 3 to 20 kilometres per hour	5 metres	

Terrestrial Areas
DO NOT apply if there are non-target vegetation or animal habitat downwind from the application area and within the **mandatory no-spray zones** shown in the table below.

Table 2 – No-Spray Zones for Protection of the Terrestrial Environment		
FOR AERIAL APPLICATION		
Wind Speed Range at Time of Application	**Downwind Mandatory No-Spray Zone**	
	Fixed-Wing	**Helicopter**
from 3 to 8 kilometres per hour	60 metres	40 metres
from 8 to 14 kilometres per hour	60 metres	60 metres
from 14 to 20 kilometres per hour	80 metres	60 metres
FOR GROUND APPLICATION		
from 3 to 20 kilometres per hour	10 metres	

Wheat and Barley

Apply to wheat and barley; from 3 leaf (BBCH 13) to full flag leaf emergence (BBCH 39)
Always apply with Uptake Spraying Oil at 500 mL/100 L

WEED	STAGE AND SIZE	RATE g /ha	CRITICAL COMMENTS
Deadnettle *(Lamium amplexicaule)*	Up to the 6 leaf stage and not more than 10 cm high	50	Do not apply after full flag leaf emergence (BBCH 39). Apply to actively growing weeds. Control may be reduced if applied to stressed weeds, regardless of the cause. Weeds emerging after treatment will not be controlled. High levels of control can generally be expected. However, some regrowth may occasionally occur. Final control may be reduced when there is good soil moisture for an extended period following application; in uncompetitive crops; or in crops planted on wide row spacing's. Final control is generally higher when weeds are small at application. Higher levels of control are likely when weeds are small at application. Control is likely to be reduced when weed density is high and limits spray coverage.
Dense-flowered fumitory *(Fumaria densiflora)*	Up to 10 cm high		
Mexican poppy *(Argemone mexicana)*	Up to the 6 leaf stage and not more than 10 cm high		
Subterranean clover *(Trifolium subterraneum)*	Up to the 6 leaf stage and not more than 8 cm in diameter		
Flax-leaf fleabane *(Conyza bonariensis)*	Up to the 6 leaf stage and not more than 6 cm in diameter	50 to 100	
Prickly lettuce *(Lactuca serriola)*	Up to the 6 leaf stage and not more than 10 cm in diameter	100	
Milk thistle / Sowthistle (*Sonchus oleraceus*); Rough sowthistle (*Sonchus asper)*	Up to the 6 leaf stage and not more than 8 cm in diameter		

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

WITHHOLDING PERIODS

Harvest: NOT REQUIRED WHEN USED AS DIRECTED.

Grazing/cutting for stockfood: DO NOT GRAZE OR CUT TREATED CROPS FOR STOCK FEED FOR 2 WEEKS AFTER APPLICATION.

LIVESTOCK DESTINED FOR EXPORT MARKETS
When GF-2685 is used as directed and the above withholding period is observed, livestock commodities are considered acceptable for export. However, export requirements are subject to change. Consult your exporter for updated information about specific market requirements. When using GF-2685 Herbicide in a tank mix with another product, observe whichever harvest or grazing/stockfood withholding period that is longer.

CROP SAFETY
Minor, transient crop effects may be observed following an application of GF-2685. Crop injury is likely to be minor, with quick recovery if crops are healthy and growing quickly at application. Recovery is likely to take longer where crop growth is limited regardless of the cause. Grain yield is normally unaffected. GF-2685 Herbicide has been tested over major commercially grown crop varieties, but not all of those that may be grown. For information on crop variety selectivity consult your local reseller or Dow AgroSciences.

GENERAL INSTRUCTIONS

RESISTANT WEEDS WARNING

GROUP	I	HERBICIDE

GF-2685 is a member of the pyridine group of herbicides. The product has the disrupters of plant cell growth mode of action. For weed resistance management, the product is a group I herbicide. Some naturally-occurring weed biotypes resistant to GF-2685 and other disrupters of plant cell growth 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 GF-2685 or other disrupters of plant growth herbicides. Since the occurrence of resistant weeds is difficult to detect prior to use, Dow AgroSciences Australia Limited accepts no liability for any losses that may result from the failure of this product to control resistant weeds. Strategies to minimize the risk of herbicide resistance are available. Consult your farm chemical supplier, consultant or the CropLife website (www.croplifeaustralia.org.au)

CROP ROTATION RECOMMENDATIONS
Safe recropping periods apply for all crops following GF-2685 application. Susceptible crops include, but are not limited to, those listed in the table below.

Re-cropping guidelines for southern Australia

Crops	Rate applied g/ha	Minimum Rainfall Required	Minimum time requirement
Wheat, Barley, Triticale, Oats, Canola	50 to 100 g	50 mm	4 weeks
Peas	50 to 100 g	75 mm	7 months
Lentils, Sub clover, Chickpeas, Faba beans, Medic, Vetch	50	100 mm	7 months
Lentils; Sub clover; Chickpeas; Faba beans; Medic; vetch	100	150 mm	7 months

Re-cropping guidelines for northern Australia

Crops	Rate applied g/ha	Minimum Rainfall Required	Minimum time requirement
Wheat, Barley, Triticale, Oats, Canola	50 to 100 g	50 mm	4 weeks
Chickpeas, Faba beans, Medic Vetch	50	150 mm	7 months
Chickpeas, Faba beans, Medic, vetch	100	200 mm	7 months

GF-2685 is primarily broken down in soil by microbial activity. Relatively quick breakdown will be associated with extended periods of soil moisture when soil temperatures are warm. Breakdown may be slow in very dry seasons, or in cold, waterlogged soils, extending the plant back interval to susceptible crops. Plant back intervals should be extended when more than 50% of the required rainfall totals consist of intermittent, light rain, which does not maintain soil wetting for at least a week.

Plant back to summer crops have not yet been established. Contact your Dow AgroSciences representative**.**

WEED DENSITY
Final control may be reduced where weed density is very high and limits spray coverage.

SPRAY COVERAGE
Control may be reduced in dense or advanced crops if spray coverage is limited.

WIDE ROW SPACINGS
Regrowth of treated weeds may be more likely where crops are grown on wide row spacings, or are un-competitive, especially if the soil remains moist for an extended period after application.

WEED GROWTH STAGE

Best results are usually achieved when applied to small weeds. Herbicide affected weeds that survive treatment may regrow when the soil remains moist for an extended period following application.

ENVIRONMENTAL CONDITIONS AT APPLICATION

Best results are usually achieved when herbicide application in made under conditions which favour rapid plant growth. Weed control may be reduced when plants are stressed by a range of factors including, but not limited to: drought, or water logging; prolonged or severe frosts; sustained high or low temperatures; poor nutrition (including deficiency and trace element toxicity); root diseases or previous herbicide application.

CONTROL OF SUBSEQUENT GERMINATIONS

GF-2685 has limited residual, pre-emergent activity and useful, reliable control of weeds germinating after application is unlikely.

APPLICATION

Apply in 80–100L/ha water by ground boom and not less than 80 L/ha by aerial application.

APVMA compliance instructions for mandatory COARSE or larger droplet size categories

Important information

These instructions inform those using this chemical product how to lawfully comply with the requirement of a COARSE or larger spray droplet size category for spray application.

Spray droplet size categories are defined in the ASAE S572 Standard (newer name may also be shown as ASABE) or the BCPC guideline. Nozzle manufacturers may refer to one or both of these documents, to identify droplet size categories; however, for a nozzle to comply with this requirement, the manufacturer must refer to at least one.

Complying with the label requirement to use a specific droplet size category means using the correct nozzle that will deliver that droplet size category under the spray operation conditions being used. The APVMA has approved only the following specific methods for choosing the correct nozzle. Use one of the methods specified in these instructions to select a correct nozzle to deliver a COARSE or larger droplet size category.

Instructions for ground application—for COARSE droplet size or larger categories
Mandatory instructions for ground applications

USE ONLY nozzles that the nozzles' manufacturer has rated to deliver a COARSE, a VERY COARSE or an EXTREMELY COARSE droplet size category, as referenced in ASAE S572 or BCPC. Choose a nozzle that is specified to provide the droplet size category required in the label Spray Drift Restraints.

DO NOT use a higher spray system pressure than the maximum the manufacturer specifies for the selected nozzle to deliver the droplet size category required in the label Spray Drift Restraint.

Instructions for fixed-wing aerial application—for COARSE droplet size or larger categories

Instructions in this section apply to fixed-wing aerial application of products for which the label Spray Drift Restraint requires a COARSE or a VERY COARSE spray droplet category.

Nozzle choices must be made using Option 1, 2 or 3 below. Option 1 nozzles are limited to a maximum aircraft speed of 110 knots and are for COARSE droplets only. Option 2 nozzles are

limited to a maximum aircraft speed of 120 knots and are also for COARSE droplets only. Option 3 nozzles have their use conditions (maximum airspeed, nozzle spray angle, product used, orifice size and spray system pressure) specified in the APVMA Approved Aerial Agricultural Association of Australia (AAAA) Nozzle Calculator (described in Option 3). Depending on those use conditions, the calculator can identify a correct nozzle for either a COARSE or a VERY COARSE spray droplet category. (To use Option 3, aerial applicators must contact the AAAA for access to their approved nozzle calculator.)

Mandatory instructions for fixed-wing aerial applications

Option 1

For up to a maximum aircraft speed of 110 knots and a COARSE droplet size category, USE ONLY solid stream 0º nozzles with orifice diameter greater than or equal to 1.5 mm and oriented straight back to the flight direction. USE ONLY a spray system pressure greater than or equal to 3 bar.

Mandatory Instructions for fixed-wing aerial applications (continued)

Option 2

For up to a maximum aircraft speed of 120 knots and a COARSE droplet size category, USE ONLY narrow angle flat fan nozzles with spray angle less than or equal to 40˚ and oriented straight back to the flight direction. USE ONLY a spray system pressure greater than or equal to 4 bar.

Mandatory instructions for fixed-wing aerial applications (continued)

Option 3

USE ONLY nozzles rated by the APVMA Approved AAAA Nozzle Calculator as COARSE or VERY COARSE to comply with a product label's requirement for a COARSE or a VERY COARSE spray droplet size category. Use the AAAA Nozzle Calculator, and follow the additional instructions below in a), b) and c).

a) To identify a nozzle to comply with the required spray droplet category, aerial applicators must use only the droplet size category given in the nozzle calculator at the DV(0.1) position. The categories shown at the DV(0.5) and the DV(0.9) positions in the calculator must not be used for making a nozzle selection.

b) Aerial applicators must not apply the product at airspeeds greater than the speed used to select the nozzle. If an application airspeed that is slower than 100 knots (the minimum speed specified in the nozzle calculator) is planned, a nozzle identified as COARSE or VERY COARSE at 100 knots can also be used at these slower airspeeds, provided that the nozzle angle and system pressure are kept the same.

c) When a particular pesticide product is chosen within the nozzle calculator as one of the conditions set to select a nozzle, then aerial applicators must use that specific pesticide product with that nozzle. When a pesticide product is planned for use and is not available as a choice within the nozzle calculator, aerial applicators must use the category 'Other product' in the calculator to set the condition for selecting a nozzle.

Instructions for helicopter aerial application—for COARSE droplet size or larger categories
Instructions in this section apply to helicopter application of products where the label Spray Drift Restraint requires a **COARSE**, a **VERY COARSE** or an **EXTREMELY COARSE** spray droplet category.

Nozzle choices must be made using Option 1, 2 or 3 below.

Mandatory instructions for helicopter aerial application

Option 1

For helicopter applications requiring a COARSE or a VERY COARSE spray droplet size category, USE ONLY nozzles selected with the methods previously specified for fixed-wing aircraft in Section 2.

Mandatory instructions for helicopter aerial Application (continued)
Option 2

When using Micronair controlled droplet applicators (Micron Sprayers Ltd), USE ONLY nozzles selected with the Micronair Droplet Size Prediction Models designed for Micronair products (and located on the company website) to choose a nozzle to satisfy the label requirement for a COARSE droplet size category. Important: to qualify for the COARSE category, the DV(0.1) value must be greater than 156 microns. Adjust parameters as necessary (eg lower the atomizer rotation rate) in order to achieve a DV(0.1) value greater than 156 microns.

Mandatory instructions for helicopter aerial application (continued)

Option 3

When using Accu-Flo nozzles (Bishop Equipment Mfg Inc), USE ONLY nozzles rated according to the manufacturer's instructions to select the correct nozzle to apply a COARSE, a VERY COARSE or an EXTREMELY COARSE droplet size category to satisfy the label requirement for one of those specific droplet size categories.

MIXING

Measure the required quantity of granules by weighing on scales. GF-2685 granules are highly soluble in water and will dissolve rapidly once added to fast moving water. **Maintain agitation at all times, including during mixing as well as spraying.**

Spray rigs with premix hoppers

For spray rigs that have a drop down chemical induction hopper, three-quarter fill this hopper with water and have the rinsing sprinkler operating. Add the GF-2685 and when dissolved, transfer this batch into the quarter filled main tank. Continue to rinse the hopper until the entire product has washed through.

Spray rigs with limited bypass agitation

For spray rigs that have limited bypass agitation, then as for most granulated formulations, pre-dissolve the GF-2685 in a bucket before adding them to the main tank. Add GF-2685 while stirring until the granules have dissolved.

Tank-mixes: The following order should be followed (wait until each formulation is mixed before adding the next one):

1. **Quarter** fill the spray tank while maintaining agitation.
2. Add GF-2685 granules, using the mixing procedure above.
3. Add LVE 600 MCPA (if required).
4. Add wettable powders, water dispersible granules or suspension concentrates.
5. Add other emulsified concentrates
6. Fill the spray tank to **half** full. Then add non-ionic surfactants or Uptake Spraying Oil.

COMPATIBILITY

Herbicides: GF-2685 is compatible with Dow AgroSciences LVE 600 MCPA Herbicide and Conclude™

Adjuvants: Apply with Uptake™ Spraying Oil. Not all surfactants and crop oils are of equal quality. Consult Dow AgroSciences before selecting other alternatives.

CLEANING SPRAY EQUIPMENT

After using GF-2685 Herbicide, empty the tank completely and drain the whole system. Thoroughly wash inside the tank using a pressure hose, drain the tank and clean tank, pump, line and nozzle filters.

After cleaning the tank as above, quarter fill the tank with clean water and circulate through the pump, line, hoses and nozzles. Drain and repeat procedure twice.

Complete Cleaning - **Decontamination** - before using sprayer to treat crops that are susceptible to GF-2685 Herbicide:

Wash the tank and rinse as above. Then, quarter fill the tank and add a standard alkali based laundry detergent at 500 g (or mL) /100 L water and circulate throughout the system for at least fifteen minutes. If useing a concentrated laundry detergent use 250 g (ormL)/100 L water. Do not use chlorine-based cleaners.

Rinse water should be discharged onto a designated disposal area or, if this is unavailable, onto unused land away from desirable plants and their roots and watercourses.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

GF-2685 is very toxic to aquatic life. **DO NOT** contaminate wetlands or watercourses with this product or used containers.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS

DO NOT apply under weather conditions or from spraying equipment that may cause spray to drift onto non-target vegetation.

Refer to MINIMUM RECROPPING PERIODS for crop rotation information. Crops susceptible to GF-2685 include but are not limited to grain legumes (summer or winter), millets (*Echinochloa* spp.), lucerne, pasture legumes; cotton, fruit, hops, ornamentals, potatoes, safflower beets, sunflower, tobacco, tomatoes, all vegetables and vines.

PROTECTION OF LIVESTOCK

- **DO NOT** graze or cut treated crops or plants for stock food except as specified under withholding periods.
- Poisonous plants may become more palatable after spraying and stock should be kept away from these plants until they have died down.

STORAGE AND DISPOSAL

- Keep out of reach of children.
- Store in the closed, original container in a securely locked, dry, cool, well-ventilated place, out of direct sunlight.
- DO NOT store near food, feedstuffs, fertilisers or seed.

500 g pack size:

- Rinse container before disposal. Add rinsings to the spray tank. Do not dispose of undiluted chemicals on site. 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.

Over 1 kg pack size:

This container can be recycled if it is clean, dry, free of visible residues and has the ***drum****MUSTER* logo visible. Triple-rinse containers for disposal. Dispose of rinsate by adding to the spray tank. Do not dispose of undiluted chemicals on site. Wash outside of the container and the cap. Store cleaned container in a sheltered place with cap removed. It will then be acceptable for recycling at any ***drum****MUSTER* collection or similar container management site. The cap should not be replaced but may be taken separately.
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.

SPILL AND LEAK MANAGEMENT

Do not touch or walk through spilled material. Dam area and prevent entry into waterways, and drains. Sweep up spilled material and place in a refuse vessel for disposal. Report large spills to Dow AgroSciences Emergency Services at 1–800 033 882.

SAFETY DIRECTIONS

May irritate the eyes and skin.
Repeated exposure may cause allergenic disorders.
Avoid contact with the eyes and skin. Sensitive workers should use protective clothing.
Wash hands after use.

FIRST AID

If poisoning occurs contact a doctor or Poisons Information Centre. Phone: Phone Australia 13 11 26; New Zealand 0800 764 766.

SAFETY DATA SHEET

Additional information is listed in the Safety Data Sheet for **GF-2685 HERBICIDE** which is available from Dow AgroSciences on request. Call Customer Service Toll Free on 1800 700 096 or visit www.dowagrosciences.com.au

EMERGENCY RESPONSE
(All Hours)
RING FROM ANYWHERE IN AUSTRALIA
1-800 033 882
(LOCAL CALL FEE ONLY)

IN A TRANSPORT EMERGENCY ONLY
DIAL 000
FOR POLICE OR FIRE BRIGADE

DOM: Batch Number:

Barcode for stock identification

APVMA Approval No: 65055/57827

Made in USA

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h	hour
ha	hectare

Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
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
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level

OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

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

REFERENCES

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