Australian Government
Australian Pesticides and Veterinary Medicines Authority

ADVICE SUMMARY

APPLICATION FOR REGISTRATION OF A CHEMICAL PRODUCT

Product name: GF-2685 HERBICIDE

Applicant: DOW AGROSCIENCES AUSTRALIA LIMITED

Product number: 65055

Application number: 57827

Purpose of Application and Description of Use: Registration of a 100 g/kg halauxifen-methyl, 100 g/kg cloquintocet-mexyl, water dispersible granule product for post-emergent control of broadleaf weeds in wheat and barley, in conjunction with the approval of halauxifen-methyl.

Active Constituent(s): CLOQUINTOCET-MEXYL

HALAUXIFEN-METHYL

Regulatory Decision:

To grant the application subject to the following conditions:

Standard Conditions of Registration/Approval

1. Containers must meet AgVet Code Regulation 18
2. Agricultural products must meet Active Constituents Quality Assurance Requirements
3. Label must contain a Date of Manufacture and Batch Number

ADVICE

Australian Government Department of Health and Ageing, Office of Chemical Safety (OCS)

OCS has conducted the public health assessment of the new active constituent halauxifen-methyl and registration of GF-2685 Herbicide containing 100 g/kg halauxifen methyl and 100 g/kg cloquinotcet-mexyl in a water dispersible granule formulation intended for post-emergent control of broadleaf weeds in wheat and barley. Halauxifen-methyl is the first member of a class of new synthetic auxin herbicides,the arylpicolinates.

The toxicology assessment of halauxifen was conducted jointly as part of a Global Joint Review (GJR) by scientists from Health Canada Pest Management Regulatory Agency (PMRA), the United States Environmental Protection Agency (EPA), and the Australia Office of Chemical Safety (OCS).

The data package provided in the submission for the product GF-2685 Herbicide comprised of six acute toxicology studies. The acute oral, dermal, inhalational toxicology studies and skin and eye irritation studies have been conducted in accordance with contemporary test guidelines and were considered adequate for the assessment of the toxicology profile of the product. The toxicology studies were conducted on halauxifen acid, with bridging studies (acute studies, rat short term, rat subchronic, rat and rabbit developmental, genotoxicity, metabolism, and immunotoxicity) performed on halauxifen methyl. The toxicology studies were conducted in accordance with contemporary test guidelines. An exposure assessment was conducted, and in conjunction with the hazard profile, was used to determine whether the proposed use of the product would be an undue health hazard to humans. In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate exposure.

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.

Acute toxicological studies demonstrated comparably low acute oral and dermal toxicity for halauxifen methyl and halauxifen acid. Neither compound was a skin irritant or a skin sensitiser (LLNA). Halauxifen methyl was not an eye irritant while halauxifen acid was a slight eye irritant. A waiver for acute inhalational toxicity studies was accepted based on the inability to generate respirable particles of either halauxifen methyl or halauxifen 29 acid. Although very similar structurally, the primary target organ of halauxifen acid is the kidney, while halauxifen methyl causes direct pre-systemic toxicity to the liver following repeat oral exposure, with liver toxicity appearing to be the more sensitive effect. *In vivo* and *in vitro* mechanistic studies were also conducted to provide information on the mode of action of liver toxicity. Based on the available liver toxicity data, including liver enzyme induction data from guideline short-term and subchronic toxicity studies in rats and *in vivo* and *in vitro* MOA studies, it was considered that 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. The rodent MOA data and *in vitro* mechanistic studies including Physiologically based Pharmacokinetic (PBPK) modelling provide evidence that humans would be

significantly less sensitive than rat to halauxifen methyl. 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.

Halauxifen methyl and halauxifen acid are not developmental toxicants and halauxifen acid did not cause reproductive toxicity. Carcinogenicity studies conducted on halauxifen acid showed no evidence of carcinogenicity, and genotoxicity studies on halauxifen acid and halauxifen methyl did not reveal any evidence of genotoxic potential. halauxifen acid was not neurotoxic in rats following acute and repeat dosing and halauxifen acid was not immunotoxic in rats. Genotoxicity studies on the metabolite did not reveal any evidence of genotoxic potential.

Based on the findings of the toxicological studies evaluated, the product has low acute oral, dermal and inhalational toxicity. It is a slight skin irritant and eye irritant. No acceptable guideline skin sensitisation study was conducted with the product. However, based on the individual acute toxicology profile of the product constituents, specifically, the active constituent cloquintocet-mexyl, the product is considered to be a potential skin sensitiser. The risk assessment also concluded that exposure to the product during mixing, loading and aerial and ground boom spray application were determined to be at acceptable levels without the use of personal protective equipment (PPE). Thus, PPE for systemic exposure is not required during use (i.e. mixing, loading and application) of the product.

The ADI for halauxifen-methyl was 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 with halauxifen-methyl and applying a 100 fold safety factor, consisting of a 10-fold safety actor for both intra- and inter-species variation. 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. Halauxifen methyl has been included in Appendix B of the Standard for the Uniform Scheduling of Medicines and Poisons with an implementation date of 1st October 2014.

The ADI for cloquintocet-mexyl is 0.04 mg/kg bw/day based on a NOEL of 4.3 mg/kg bw/day for thyroid follicular epithelium hyperplasia in females at 41.3 mg/kg bw/day and above in a 2-year rat study and using a 100 fold safety factor. The ADI was established in 1994. No ARfD has been established for cloquintocet-mexyl and no data were submitted to enable an ARfD to be set. Cloquintocet-mexyl is currently listed in Schedule 5 of the SUSMP with no cut-off concentrations.

This product contains 10% halauxifen (as methyl ester) and 10% cloquintocet-mexyl and is therefore included in Schedule 5. Based on the toxicology profile of the product, this classification is considered appropriate.

Based on the findings of the toxicological studies evaluated, the product has low acute oral, dermal and inhalational toxicity. It is a slight skin irritant and eye irritant. Considering the individual acute toxicology profile of the product constituents, specifically, the active constituent cloquintocet-mexyl, the product is considered to be a potential skin sensitiser.

Based on the outcomes of the risk assessment, First Aid Instructions and Safety Directions have been recommended for inclusion on the product label. The toxicology data and other information provided and considered in this assessment justify the recommendations established in the present evaluation.

After consideration of the hazards associated with the proposed product, along with the exposure and risks expected with use of the proposed product, the OCS recommended that the proposed use of GF-2685 Herbicide containing 100 g/L of halauxifen methyl and 100 g/L cloquintocet-mexyl will not be an undue health hazard to humans according to the criteria stipulated in Section 14 of the Ag/Vet Code Act of 1994.

Based on the advice from the OCS in regards to the toxicology and occupational health and safety and the label was amended to incorporate the above recommendations, the APVMA is satisfied that there should be no adverse effects on human health from the use of GF-2685 Herbicide when used in accordance with the proposed label directions.

Data relied on to provide the advice

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71259	I	Stebbins, K.E. et al	XDE-729: 28-Day Dermal Toxicity Study in F344/DuCrl Rats	2010	Toxicology	Acute dermal studies, active	Dow Agrosciences Australia Limited	57828
71242	I	Durando, J.	Acute Dermal Toxicity Study in Rats	2011	Toxicology	Acute dermal studies, active	Dow Agrosciences Australia Limited	57828
71241	I	Durando, J.	Acute Dermal Toxicity Study In Rats	2009	Toxicology	Acute dermal studies, active	Dow Agrosciences Australia Limited	57828
71193	S	Durando, J.	Acute Dermal Toxicity Study in Rats	2012	Toxicology	Acute dermal studies, product	Applicant	
71246	I	Durando, J.	Primary Eye Irritation Study in Rabbits	2010	Toxicology	Acute eye irritation studies, active	Dow Agrosciences Australia Limited	57828
71247	I	Durando, J.	Primary Eye Irritation Study in Rabbits	2011	Toxicology	Acute eye irritation studies, active	Dow Agrosciences Australia Limited	57828
71196	S	Durando, J.	Primary Eye Irritation Study in Rabbits	2011	Toxicology	Acute eye irritation studies, product	Applicant	
71243	I	Kreiger, S.M., Garlinghouse, C.R.	XDE-729 and XDE-729 methyl: Acute Dust Aerosol Inhalation Toxicity Studies in F344/DUCRL Rats	2011	Toxicology	Acute inhalation studies, active	Dow Agrosciences Australia Limited	57828
71194	S	Krieger, SM and Garlinghouse, CR	GF-2685: Acute Dust Aerosol Inhalation Toxicity Study in F344/DuCrl Rats	2011	Toxicology	Acute inhalation studies, product	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71240	I	Durando, J.	Acute Oral Toxicity Up and Down Procedure in Rats	2011	Toxicology	Acute oral studies, active	Dow Agrosciences Australia Limited	57828
71192	S	Durando, J.	Acute Oral Toxicity Up and Down Procedure in Rats	2012	Toxicology	Acute oral studies, product	Applicant	
71244	I	Durando, J.	Primary skin irritation study in rabbits	2009	Toxicology	Acute skin irritation studies, active	Dow Agrosciences Australia Limited	57828
71245	I	Durando, J.	Primary skin irritation study in rabbits	2011	Toxicology	Acute skin irritation studies, active	DOW AGROSCIENCES AUSTRALIA LIMITED	57828
71195	S	Durando, J.	Primary Skin Irritation Study in Rabbits	2011	Toxicology	Acute skin irritation studies, product	Applicant	
71249	I	Boverhof, D.R., Sosinski, L.K.	XDE-729 methyl: Local Lymph Node Assay in CBA/J Mice	2011	Toxicology	Acute skin sensitisation studies, active	Dow Agrosciences Australia Limited	57828
71248	I	Boverhof, D.R., Sosinski, L.K.	XR-729: Local Lymph Node Assay in CBA/J Mice	2011	Toxicology	Acute skin sensitisation studies, active	Dow Agrosciences Australia Limited	57828
71270	I	Stebbins, K.E. et al	XDE-729: Two-Year Chronic Toxicity/Oncogenicity Study in F344/DuCrl Rats	2012	Toxicology	Chronic/ carcinogenicity studies	Dow Agrosciences Australia Limited	57828
71271	I	Thomas, J. et al	XDE-729: 18-Month Dietary Oncogenicity Stuidy in Crl:CD1(ICR) Mice	2012	Toxicology	Chronic /carcinogenicity studies	Dow Agrosciences Australia Limited	57828
71258	I	Heward, J.	XDE-729: 1 Year Oral (Dietary) Toxicity Study in Beagle Dogs	2012	Toxicology	Chronic/carcinogenicity studies	Dow Agrosciences Australia Limited	57828
71285	I	Ellis-Hutchings, R.G. et al	XDE-729: Dietary Developmental Toxicity Study in New Zealand White Rabbits	2011	Toxicology	Developmental (teratology) studies	Dow Agrosciences Australia Limited	57828

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71284	I	Ellis-Hutchings, R.G. et al	XDE-729: Dietary Developmental Toxicity Probe Study in New Zealand White Rabbits	2011	Toxicology	Developmental (teratology) studies	Dow Agrosciences Australia Limited	57828
71283	I	Ellis-Hutchings, R.G. et al	XDE-729 methyl: Dietary Developmental Toxicity Study in Crl:CD (SD) Rats	2012	Toxicology	Developmental (teratology) studies	Dow Agrosciences Australia Limited	57828
71282	I	Ellis-Hutchings, R.G. et al	XDE-729 methyl: Dietary Developmental Toxicity Probe Study in Crl:CD (SD) Rats	2012	Toxicology	Developmental (teratology) studies	Dow Agrosciences Australia Limited	57828
71287	I	Ellis-Hutchings, R.G. et al	XDE-729 Methyl: Developmental Toxicity Study in New Zealand White Rabbits	2012	Toxicology	Developmental (teratology) studies	Dow Agrosciences Australia Limited	57828
71286	I	Ellis-Hutchings, R.G. et al	XDE-729 Methyl: Developmental Toxicity Probe Study in New Zealand White Rabbits	2012	Toxicology	Developmental (teratology) studies	Dow Agrosciences Australia Limited	57828
71281	I	Ellis-Hutchings, R.G., Marshall, V.A.	XDE-729: Dietary Developmental Toxicity Study in Crl:CD (SD) Rats	2010	Toxicology	Developmental (teratology) studies	Dow Agrosciences Australia Limited	57828
71260	I	Dakoulas, E. M. and VanDyke, M. R.	Salmonella - Escherichia coli, Mammalian-microsome reverse mutation assay preincubation method with a confirmatory assay with XDE-729	2010	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71261	I	Dakoulas, E. M. and VanDyke, M. R.	Salmonella - Escherichia coli, Mammalian-microsome reverse mutation assay preincubation method with a confirmatory assay with XDE-729 methyl	2011	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71262	I	Nagane, R.M.	Bacterial Reverse Mutation Test of XDE-729 Methyl TGAI Using Salmonella Typhimurium	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71263	I	Schisler, M. R.	Evaluation of XDE-729 (4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-2-pyridinecarboxylic acid) in an in vitro chromosomal aberration assay utilizing rat lymphocytes	2010	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71264	I	Schisler, M.R.	Evaluation of XDE-729 methyl in an in vitro chromosomal aberration assay utilizing rat lymphocytes	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71265	I	Nagane, R.M.	In vitro Mammalian Chromosome Aberration Test of XDE-729 Methyl TGAI in Human Peripheral Blood Lymphocytes	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71266	I	Schisler, M. R., LeBaron, M.J.	Evaluation of XDE-729 in the Chinese Hamster Ovary Cell-Hypoxanthine-Guanine-phosphoribosyl transferase (CHO-HGPRT) Forward Mutation Assay	2010	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71267	I	Schisler, M.R	Evaluatiuon of XDE-729 Methyl in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay	2011	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71268	I	Nagane, R.M.	In vitro Mammalian Cell Gene Forward Mutation Test at the HGPRT Locus of the Chinese Hamster Ovary (CHO)-K1 Cell Line using XDE-729 Methyl TGAI	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71269	I	Schisler, M. R.	Evaluation of XDE-729 (4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-2-pyridinecarboxylic acid) in the mouse peripheral blood micronucleus assay	2010	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71291	I	Nagane, R.M.	In Vitro Mamalian Cell Gene Forward Mutation Test at the HGPRT Locus of the Chinese Hamster Ovary (CHO)-K1 Cell Line Using X11449757	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71292	I	Nagane, R.M.	In Vitro Mammalian Chromosome Aberration Test if X11449757 in Human Peripheral Blood Lymphocytes	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71272	I	LeBaron, M.J. et al	Hepatic Gene Expression and Biomarker Analyses in Male F344/DuCrl Rats Administered XDE-729 or XDE-729 Methyl for Seven Days	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71290	I	Nagane, R.M.	Bacterial Reverse Mutation Test of X11449757 using Salmonella typhimurium	2012	Toxicology	Genotoxicity (mutagenicity) studies	Dow Agrosciences Australia Limited	57828
71294	I	Lu, H.	XDE-729 Methyl Toxicology Overview	2012	Toxicology	Other information	Dow Agrosciences Australia Limited	57828

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71279	I	Carney, E. W. et al	XDE-729: A Reproduction/Developmental Toxicity Probe Study in Crl:CD(SD) Rats	2010	Toxicology	Reproduction studies	Dow Agrosciences Australia Limited	57828
71280	I	Rasoulpour, R.J. et al	XDE-729: Two Generation Dietary Reproductive Toxicity Study in CRL:CD (SD) Rats	2011	Toxicology	Reproduction studies	Dow Agrosciences Australia Limited	57828
71251	I	Stebbins, K.E., Marshall, V.A., McCoy, A.T.	XDE-729 Methyl: 28-day Dietary Toxicity Study in F344/DuCrl Rats	2011	Toxicology	Short-term studies	Dow Agrosciences Australia Limited	57828
71250	I	Yano, B. L. et al	XR-729: 28-day Dietary Toxicity Study in F344/DUCRL Rats	2009	Toxicology	Short-term studies	Dow Agrosciences Australia Limited	57828
71253	I	Popke, E.J.	XR-729: Palatability Probe and 28-Day Dietary Toxicity Study in Beagle Dogs	2010	Toxicology	Short-term studies	Dow Agrosciences Australia Limited	57828
71252	I	Thomas, J. et al	XR-729: 28-Day Dietary Toxicity Study in Crl:CD1(ICR) Mice	2009	Toxicology	Short-term studies	Dow Agrosciences Australia Limited	57828
71273	I	Sura, R. et al	XDE-729 Methyl: 7Day Dietary Toxicity Probe Study on Crl:CD1 ICR Mice	2012	Toxicology	Short-term studies	Dow Agrosciences Australia Limited	57828
71278	I	Murphy, L.A. et al	XDE-729 Methyl: Mode of Action and Human Relevance Framework Analysis for XDE-729 Methyl-Induced Rodent Liver Effects	2012	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828
71198	S	De Bie, A.Th.H.J.	In Vivo percutaneous absorption of [14C]XR-729 methyl, Formulated as GF-2573 in Rats	2011	Toxicology	Studies of other special effects	Applicant	
71199	S	van Meeuwen, R.N.C. and de Ligt, R.A.F.	In Vitro Percutaneous Absorption of [14C]XR-729 methyl, Formulated as GF-2573 through Human and Rat Skin Membranes	2011	Toxicology	Studies of other special effects	Applicant	
71277	I	Rick, D.L., McFadden, J.R., McClymont, E.L.	XDE 729 Methyl: Determination of In vitro Hydrolysis rates in Liver 59, Blood and Synthetic Gastric Fluid of Mouse, Rat and Human and Physiologically-Based Pharmacokinetic Simulations of Systemic Exposure in Rats and Humans	2012	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828
71276	I	Murphy, L.A.	In Vitro Assessment of AhR (ARYL Hydrocarbon Receptor) Nuclear Receptor Activation and CYP 1A and Cyp 1a Induction Potential of XDE-729 Methyl in Primary Hepatocyte Cultures	2012	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71275	I	Perdew, G.H.	XDE-729 Methyl: Evaluation of AHR Activation Potential of XDE-729 Methyl via Luciferase Reporter and Ligand Binding Assays	2012	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828
71288	I	Marty, M. S., Andrus, A. K. and Sura, R.	XDE-729: Acute Neurotoxicity in F344/DuCrl Rats	2010	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828
71289	I	Marty, M. S., Andrus, A. K. and Sura, R.	XDE-729: 90-Day Dietary Neurotoxicity Study in F344/DuCrl Rats	2011	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828
71293	I	Boverhof, D.R. et al	XDE-729 Methyl: Asessment of Immunotoxic Potential Using the Sheep Red Blood Cell Assay after 28-Day Dietary Exposure to Female F344/DuCrl Rats	2012	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828
71274	I	Boverhof, D.R. et al	XDE-729 Methyl: Evaluation of Molecular and Cellular Changes in the Livers of Male F344/DuCrl Rats after a Four Week Dietary Exposure and a Four Day or 28 Day Recovery Period.	2012	Toxicology	Studies of other special effects	Dow Agrosciences Australia Limited	57828
71257	I	Heward, J.K.	XDE-729: A 90-Day Oral (Dietary) Toxicity Study in Beagle Dogs	2011	Toxicology	Sub-chronic studies	Dow Agrosciences Australia Limited	57828
71256	I	Thomas, J. et al	XDE-729: 90-Day Dietary Toxicity Study in Crl:CD1(ICR) Mice	2010	Toxicology	Sub-chronic studies	Dow Agrosciences Australia Limited	57828
71254	I	Yano, B.L. et al	XDE-729: 90-Day Dietary Toxicity Study in F344/DUCRL Rats	2010	Toxicology	Sub-chronic studies	Dow Agrosciences Australia Limited	57828
71255	I	Stebins, K.E. et al	XDE-729 Methyl: 90-Day Dietary Toxicity Study in DuCrl/F344 Rats	2012	Toxicology	Sub-chronic studies	Dow Agrosciences Australia Limited	57828

Australian Government Department of Environment

The Department of the Environment has assessed data in support of the proposed use of the new product, GF-2685 Herbicide, containing the new active constituent, halauxifen-methyl and the currently registered crop safener, cloquintocet-mexyl, for the control of broadleaf weeds in wheat and barley.

The assessment indicated that Halauxifen-methyl is generally stable to hydrolysis but may undergo aqueous photolytic degradation. It undergoes degradation by biotic processes in both soil and water under both aerobic and anaerobic laboratory conditions and dissipates quickly from the aquatic water and sediment

compartments. Under field conditions the substance also degrades with field dissipation rates generally higher to degradation rates found under laboratory conditions, but still not sufficient to consider the substance persistent. Halauxifen-methyl is unlikely to bioaccumulate.

Halauxifen-methyl is practically non-toxic to birds based on acute and dietary exposure. No effects on avian reproduction are expected based on application rates and uses assessed. It was found to be moderately toxic to fish and aquatic invertebrates based on both acute and chronic exposure. Halauxifen-methyl was moderately toxic to four standard algal test species and the standard floating aquatic macropyte, *Lemna gibba*. However, it was very toxic to the rooted aquatic macrophyte, *Myriophyllum spicatum*. This very high toxicity was observed in testing using both the active constituent and formulated end-use product. Metabolites were generally less toxic than the parent substance. However, the main acid metabolite showed toxicity to the rooted aquatic macrophyte almost as high as the parent compound.

Halauxifen-methyl generally did not exhibit toxicity towards terrestrial invertebrates (bees, soil dwelling organisms or non-target arthropods) or soil microorganisms. Testing using the formulated end-use product showed terrestrial plants to be more sensitive when exposed through foliar application rather than pre-emergence application to soil.

The risk assessment therefore concluded that the proposed product is unlikely to pose an environmental risk under the proposed use pattern and recommended appropriate down-wind spray drift buffer zones for the protection of sensitive aquatic and terrestrial areas.

The recommended label amendments have been incorporated to the label and therefore the APVMA is satisfied that the use of GF-2685 Herbicide as proposed would not be likely to have an unintended effect that is harmful to animals, plants or things, or to the environment.

Data relied on to provide the advice

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71115	S	Yoder, R.N., Boulton, J.	Soil Degradation of XDE-729 Methyl under Anaerobic, Low Temperature and Sterile Conditions	2011	Environment fate	Biodegradation soils	Applicant	
71114	S	Yoder, R.N., et al	Soil Degradation of XDE-729 Methyl under Aerobic Conditions on Four Global Soils- AMENDMENT	2011	Environment fate	Biodegradation soils	Applicant	
71120	S	Yoder, R.N., Lehman, A.C., Balcer, J.L.	Anaerobic Aquatic Degradation of XDE-729 Methyl in Two US Sediment and Pond Water Systems	2012	Environment fate	Biodegradation water	Applicant	
71121	S	Laughlin, L.A., Balcer, J.L.	Aerobic Transformation of XDE-729 Methyl in Two Aquatic Sediment Systems-AMENDED REPORT	2012	Environment fate	Biodegradation water	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71059	S	Kellner, T.	Soil dissipation study with one autumn application of XDE-729 as GF-2573 at four sites in Northern and Southern Europe in 2010-2012	2012	Environment fate	Field dissipation soils	Applicant	
71117	S	Newcombe, A.C., Negley, T.L., van Wesenbeeck, I.J.	Dissipation of XDE-729 in Soil under Cropped and Bare Soil Conditions at Multiple Sites Across North America	2012	Environment fate	Field dissipation soils	Applicant	
71060	S	Kellner, T.	Soil dissipation study with one spring application of XDE-729 as GF-2573 at four sites in Northern and Southern Europe in 2010-2011	2012	Environment fate	Field dissipation soils	Applicant	
71118	S	Yoder, R.N., Smith, K.P., Adusumilli, H.	Batch Equilibrium Study Adsorption/Desorption of XDE-729 Methyl and Adsoption of its X11393729 and X11449757 Metabolites (Amended Report)	2011	Environment fate	Mobility adsorption/desorption	Applicant	
71116	S	Ma, M., Adelfinskaya, Y.A.	Photodegradation of XDE-729 Methyl on Soil	2011	Environment fate	Physicochemical degradation photodegradation	Applicant	
71137	S	Rebstock, M	XDE-729 Methyl: Acute Toxicity to the Water Flea, Daphnia magna, Determined Under Static Test Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71074	S	Rebstock, M.	GF-2685: Growth Inhibition Test with the Freshwater Aquatic Plant, Duckweed, Lemna gibba	2012	Environment toxicology	Aquatic organisms acute	Applicant	
71179	S	Dinehart, S.	XDE-729 Methyl: Acute toxicity to the Tadpole (Xenopus laevis) determined under flow through test conditions	2012	Environment toxicology	Aquatic organisms acute	Applicant	
71073	S	Gosnier, G.	GF-2573 - Growth Inhibition of Myriophyllim spicatum in a Water/Sediment System	2012	Environment toxicology	Aquatic organisms acute	Applicant	
71172	S	Gerke, A.	XDE-729 Methyl: Whole sediment acute toxicity to a marine amphipod (Leptocheirus plumulosis)	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71140	S	Gaertner, K.	X11406790 (XDE-729 Metabolite): Acute Toxicity to the Cladoceran, Daphnia magna, Determined Under Static Test Conditions	2012	Environment toxicology	Aquatic organisms acute	Applicant	
71071	S	Rebstock, M.	GF-2685: Growth Inhibition Test with the Unicellular Green Alga, Pseudokirchneriella subcapitata	2012	Environment toxicology	Aquatic organisms acute	Applicant	
71139	S	Bergfield, A	X11449757: Acute Toxicity to the Water Flea, Daphnia magna, Determined Under Static-Renewal Test Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71132	S	Gaertner, K.	X11406790 (XDE-729 Metabolite): Acute Toxicity to the Rainbow Trout, Oncorhynchus mykiss, Determined Under Static-Renewal Test Conditions	2012	Environment toxicology	Aquatic organisms acute	Applicant	
71170	S	Bergfield, A	XDE-729 Methyl: Acute Toxicity Test with the Mysid Shrimp, Americamysis bahia, Determined Under Flow-Through Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71169	S	Gerke, A.	XDE-729 Methyl: Acute Toxicity to the Sheepshead Minnow, Cyprinodon variegatus, Determined Under Flow-Through Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71154	S	Gerke, A	XDE-729 Methyl: Whole Sediment 10 Day Acute Toxicity Test with Midge Larvae (Chironomus dilutus)	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71131	S	Bergfield, A.	X11449757: Acute Toxicity to the Rainbow Trout, Oncorhynchus mykiss, Determined Under Static-Renewal Test Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71130	S	Rebstock M	XDE-729 Acid: Acute Toxicity to the Rainbow Trout, Oncorhynchus mykiss, Determined Under Static-Renewal Test Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71128	S	Gerke A	XDE-729 Methyl: Acute Toxicity to the Rainbow Trout, Oncorhynchus mykiss, Determined Under Static-Renewal Test Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71129	S	Rebstock, M	XDE-729 Methyl: Acute Toxicity to the Fathead Minnow, Pimephales promelas, Determined Under Static-Renewal Test Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71138	S	Bergfield, A	XDE-729 Acid: Acute Toxicity to the Water Flea, Daphnia magna, Determined Under Static-Renewal Test Conditions	2011	Environment toxicology	Aquatic organisms acute	Applicant	
71171	S	Hicks S.L	XDE-729 Methyl: Effect on New Shell Growth of the Eastern Oyster (Crassostrea virginica)	2011	Environment toxicology	Aquatic organisms other	Applicant	
71141	S	Bergfield, A	XDE-729 Methyl: Chronic Toxicity with the Water Flea, Daphnia magna, Exposed Under Static-Renewal Test Conditions	2011	Environment toxicology	Aquatic organisms other	Applicant	
71173	S	Dinehart, S.	XDE-729 Methyl: Early Life Stage Toxicity Test with the Sheepshead Minnow, Cyprinodon variegatus, Under Flow Thorugh Conditions	2012	Environment toxicology	Aquatic organisms other	Applicant	
71174	S	Hicks S.L	XDE-729 Methyl: Life-Cycle Toxicity Test of the Saltwater Mysid, Americamysis bahia, Conducted under Flow-Through Conditions	2011	Environment toxicology	Aquatic organisms other	Applicant	
71182	S	Palmer, S.J. et al	XDE-729 Methyl: Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances	2012	Environment toxicology	Aquatic organisms other	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71143	S	Gerke, A	XDE-729 Methyl: Chronic Toxicity in Whole Sediment to Freshwater Midge, Chironomus riparius	2011	Environment toxicology	Aquatic organisms other	Applicant	
71142	S	Bergfield, A.	XDE-729 Acid: Chronic Toxicity Test with the Water Flea, Daphnia magna, Exposed Under Static-Renewal Conditions	2011	Environment toxicology	Aquatic organisms other	Applicant	
71135	S	Gerke, A	XDE-729 Acid: Early Life-Stage Toxicity Test with the Fathead Minnow, Pimephales promelas, Under Flow-Through Conditions	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71134	S	Gerke, A	XDE-729 Methyl: Early Life-Stage Toxicity Test with the Fathead Minnow, Pimephales promelas, Under Flow-Through Test Conditions	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71133	S	Dinehart, S.	X11449757: Early Life-Stage Toxicity Test with the Fathead Minnow, Pimephales promelas, Under Flow-Through Conditions	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71162	S	Gonsior, G.	X11406790: Growth Inhibition of Myriophyllum spicatum in a Water/Sediment System.	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71161	S	Gonsior, G.	X11449757: Growth Inhibition of Myriophyllum spicatum in a Water/Sediment System.	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71144	S	Weber, K.	Testing of Effects of XDE-729 Methyl on the Single Cell Green Alga Pseudokirchneriella subcapitata in a 96 h static test.	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71145	S	Rebstock, M	XDE-729 Methyl: Growth Inhibition Test with the Freshwater Diatom, Navicula pelliculosa	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71146	S	Weber, K.	Testing of Effects of XDE-729 Methyl on the Blue-Green Alga, Anabaena flos-aquae, in a 96 h Static Test	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71147	S	Rebstock, M	XDE-729 Methyl: Static Growth Inhibition Test with the Marine Diatom, Skeletonema costatum	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71148	S	Rebstock, M.	XDE-729 Acid: Growth Inhibition Test with the Unicellular Green Alga, Pseudokirchneriella subcapitata	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71149	S	Rebstock, M.	XDE-729 Acid: Growth Inhibition Test with the Freshwater Diatom, Navicula pelliculosa	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71150	S	Rebstock, M.	XDE-729 Acid: Growth Inhibition Test with the Blue-Green Alga, Anabaena flos-aquae	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71151	S	Rebstock, M.	XDE-729 Acid: Static Growth Inhibition Test with the Marine Diatom, Skeletonema costatum	2011	Environment toxicology	Aquatic organisms short-term	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71152	S	Rebstock, M	X11449757: Growth Inhibition Test with the Unicellular Green Alga, Pseudokirchneriella subcapitata	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71153	S	Rebstock, M.	X11406790: Growth Inhibition Test with the Unicellular Green Alga, Pseudokirchneriella subcapitata	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71160	S	Gonsoir, G.	XDE-729 Acid: Growth Inhibition of Myriophyllum spicatum in a Water/Sediment System.	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71155	S	Rebstock, M	XDE-729 Methyl: Growth Inhibition Test with the Freshwater Aquatic Plant, Duckweed, Lemna gibba	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71156	S	Rebstock, M	XDE-729 Acid: Growth Inhibition Test with the Freshwater Aquatic Plant, Duckweed, Lemna gibba	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71157	S	Rebstock, M.	X11449757: Growth Inhibition Test with the Freshwater Aquatic Plant, Duckweed, Lemna gibba	2011	Environment toxicology	Aquatic organisms short-term	Applicant	
71158	S	Rebstock, M.	X11406790: Growth Inhibition Test with the Freshwater Aquatic Plant, Duckweed, Lemna gibba	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71159	S	Gonsior, G.	XDE-729 Methyl - Growth Inhibition of Myriophyllum spicatum in a Water/Sediment System	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71180	S	Palmer, S.J. et al	XDE-729 Methyl: Fish Short-Term Reproduction Assay with the Fathead Minnow (Pimephales promelas)	2012	Environment toxicology	Aquatic organisms short-term	Applicant	
71163	S	Schmitzer, S.	Effects of XDE-729 Methyl (Acute Contact and Oral) on Honey Bees (Apis mellifera L.) in the Laboratory	2011	Environment toxicology	Non-target invertebrates (terrestrial) bees	Applicant	
71184	S	Witte, B.	Effects of XDE-729 Methyl on Reproduction and Growth of Earthworms Eisenia fetida in Artificial Soil with 5% Peat	2010	Environment toxicology	Non-target invertebrates (terrestrial) earthworms	Applicant	
71183	S	Witte, B.	Effects of XDE-729 Acid on Reproduction and Growth of Earthworms Eisenia fetida in Artificial Soil with 5% Peat	2010	Environment toxicology	Non-target invertebrates (terrestrial) earthworms	Applicant	
71185	S	McCormac, A.	Determination of the chronic (sub-lethal) toxicity of aged residues of technical-grade XDE-729 Methyl to the earthworm Eisenia fetida in two natural soil substrates	2012	Environment toxicology	Non-target invertebrates (terrestrial) earthworms	Applicant	
71168	S	Witte, B	Acute Toxicity (14 Days) of X11449757 (metabolite of XDE-729) of the Earthworm Eisenia fetida in Artificial Soil with 5% Peat	2010	Environment toxicology	Non-target invertebrates (terrestrial) earthworms	Applicant	
71166	S	Witte, B	XDE-729 Methyl: Acute Toxicity (14 days) of XDE-729 Methyl to the Earthworm Eisenia fetida in Artificial Soil with 5% Peat	2011	Environment toxicology	Non-target invertebrates (terrestrial) earthworms	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71167	S	Witte, B	Acute Toxicity (14 Days) of XDE-729 Acid to the Earthworm Eisenia fetida in Artificial Soil with 5% Peat	2011	Environment toxicology	Non-target invertebrates (terrestrial) earthworms	Applicant	
71186	S	Witte, B.	Effects of X11449757 (a metabolite of XDE-729) on Reproduction and Growth of Earthworms Eisenia fetida in Artificial Soil with 5% Peat	2010	Environment toxicology	Non-target invertebrates (terrestrial) earthworms	Applicant	
71067	S	Witte, B.	Effects of XDE-729 Acid on Reproduction of the Collembola Folsomia candidain Artificial Soil with 5% Peat.	2011	Environment toxicology	Non-target invertebrates (terrestrial) other	Applicant	
71068	S	Gerke, A.	X11449757: Inhibition of Reproduction of Collembola, Folsomia candida, in Artificial Soil	2011	Environment toxicology	Non-target invertebrates (terrestrial) other	Applicant	
71165	S	Gerke, A.	XDE-729 Methyl: Inhibition of Reproduction of Collembola, Folsomia candida, in Artificial Soil	2011	Environment toxicology	Non-target invertebrates (terrestrial) other	Applicant	
71072	S	Moll, M.	Effects of GF-2685 on the Parasitoid Aphidius rhopalosiphi in the Laboratory (Tier I) - Dose Response Test -	2012	Environment toxicology	Non-target invertebrates (terrestrial) parasites	Applicant	
71066	S	Witte, B.	Effects of X11449757 (metabolite of XDE-729) on Reproduction of the Predatory Mite Hypoaspis aculeifer in Artificial Soil with 5% Peat	2011	Environment toxicology	Non-target invertebrates (terrestrial) predators	Applicant	
71065	S	Witte, B.	Effects of XDE-729 Acid on Reproduction of the Predatory Mite, Hypoaspis aculeifer, in Artificial Soil with 5% Peat	2011	Environment toxicology	Non-target invertebrates (terrestrial) predators	Applicant	
71164	S	Luhrs, U.	Effects of XDE-729 Methyl on Reproduction of the predatory mite Hypoaspis aculeifer in Artificial Soil with 5% Peat	2011	Environment toxicology	Non-target invertebrates (terrestrial) predators	Applicant	
71064	S	Schwarz, A.	Effects of GF-2685 on the Predatory Mite Typhlodromus pyri in the Laboratory (Tier I) - Dose Response Test	2012	Environment toxicology	Non-target invertebrates (terrestrial) predators	Applicant	
71061	S	Feil, N.	Effects of XR-729 methyl on the activity of the soil microflora in the laboratory	2011	Environment toxicology	Non-target invertebrates (terrestrial) soil micros	Applicant	
71063	S	Feil, N.	Effects of X11449757 on the Activity of the Soil microflora in the Laboratory.	2011	Environment toxicology	Non-target invertebrates (terrestrial) soil micros	Applicant	
71062	S	Feil, N.	XDE-729: Effects of XDE-729 acid on the activity of the soil microflora in the laboratory	2010	Environment toxicology	Non-target invertebrates (terrestrial) soil micros	Applicant	
71176	S	Bergfield, A.	GF-2685: Effects on the Vegetative Vigor of Non-Target Terrestrial Plants (Tier II)	2012	Environment toxicology	Non-target vegetation - laboratory	Applicant	
71178	S	Rockcliff, C.	Evaluation of the Phytotoxicity of the XDE-729 M-757 metabolite GLP Seedling Emergence and Seedling Growth Test Terrestrial Non Target Plants (Based on OECD Guideline 208) - Europe 2011	2011	Environment toxicology	Non-target vegetation - laboratory	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71177	S	Rockcliffe, C.	Evaluation of the Phytotoxicity of the XDE-729 acid GLP Seedling Emergence and Seedling Growth Test Terrestrial Non Target Plants (Based on OECD Guideline 208) - Europe 2011	2011	Environment toxicology	Non-target vegetation - laboratory	Applicant	
71175	S	Bergfield, A.	GF-2685: Effects on the Seedling Emergence and Growth of Non-Target Terrestrial Plants (Tier II)	2011	Environment toxicology	Non-target vegetation - laboratory	Applicant	
71123	S	Hubbard, P.M., Beavers, J.B.	XDE-729 Methyl: An Acute Oral Toxicity Study with the Zebra Finch (Poephila guttata)	2011	Environment toxicology	Vertebrates acute	Applicant	
71122	S	Hubbard, P., Beavers, J.B	XDE-729 Methyl: An Acute Oral Toxicity Study with the Northern Bobwhite.	2011	Environment toxicology	Vertebrates acute	Applicant	
71126	S	Temple, D.L.; Martin, K.H.; Beavers, J.B.; Jaber, M	XDE-729 Methyl: A Reproduction Study with the Northern Bobwhite	2011	Environment toxicology	Vertebrates other	Applicant	
71127	S	Temple, D.L.; Martin, K.H.; Beavers, J.B.; Jaber, M	XDE-729 Methyl: A Reproduction Study with the Mallard	2011	Environment toxicology	Vertebrates other	Applicant	
71125	S	Hubbard, P. M; Martin, K. H; Beavers, J.B	XDE-729 Methyl: A Dietary LC50 Study with the Mallard	2011	Environment toxicology	Vertebrates short-term	Applicant	
71124	S	Hubbard, P. M; Martin, K. H; Beavers, J.B	XDE-729 Methyl: A Dietary LC50 Study with the Northern Bobwhite	2011	Environment toxicology	Vertebrates short-term	Applicant	
71094	S	Hansen, S. C. et al	XDE-729 and XDE-729 methyl: Pharmacokinetics and Metabolism in F344/DuCrl Rats	2010	Metabolism and kinetics	Laboratory animals	Applicant	
71093	S	Johnson, T.L.	An Investigation of [14C]-Labeled XDE-729 Metabolism and Excretion Balance in Beagle Dogs Following a Single Oral (Gavage) Administration	2012	Metabolism and kinetics	Laboratory animals	Applicant	
71092	S	Saghir, S.A., Clark, A.J., Brzak, K.A.	XR-729: Probe Study to Determine Absorption, Distribution, Metabolism, and Elimination in F344/DUCRL Rats and CRL:CS1(ICR) Mice	2011	Metabolism and kinetics	Laboratory animals	Applicant	

APVMA Residues Team

APVMA Pesticides Residues Section (PRS) has evaluated the available metabolism, residue trials, analytical methodology, fate in storage, processing data and residues in trade issues.

Data from metabolism studies conducted in wheat, turnips, rotational crops (wheat, lettuce and radishes), rats, lactating goats, and laying hens. A large package of residues trials conducted in Australia and New Zealand for wheat, barley and oats (over the 2010 and 2011 seasons), and in the USA and Canada for wheat and barley (during the 2010 and 2011 seasons) were presented. All trials were conducted in accordance with Good Laboratory Practice (GLP), and were well supported by detailed analytical methods and sample storage stability data. In the Australian and New Zealand cereal trials, a single application of GF-2685 Herbicide was made at growth stage BBCH 39 (full flag leaf emergence, the latest stage at which application is proposed). As the GAPs used in the trials for wheat, barley and oats are the same, the residue data for the three cereals can be combined for determining MRLs. A processing study for wheat was conducted in the USA, with grain from crops treated at 5× the normal rate being processed into a range of processed wheat commodities using simulated commercial processes. Data was provided from a feeding study using lactating Holstein/Friesian dairy cattle involved dosing the animals orally daily for 28-29 consecutive days with halauxifen-methyl at target feeding levels of 1, 3, and 15 ppm dry matter in feed.

Considering the assessment, the Given that:

- in the wheat metabolism study, parent compound was present at similar levels to the other residue components in forage, hay and straw while all components in the edible portion (grain) were below the LOQ;
- in the turnip metabolism study, parent compound was a significant component of the residue;
- no individual residue components were found above the LOQ in the rotational crop metabolism study; and
- in the field residue trials in cereals, no residues were found above the LOQ in grain, while parent compound was found more often than halauxifen acid and at significantly higher levels in forage samples,

a simple residue definition for compliance purposes is warranted. Parent compound is a suitable marker residue, as in almost all cases in the field trials and metabolism studies, where any residue components were quantifiable, parent was one of those components, and often the only component in the field trials.

proposed residue definition for halauxifen-methyl for the purposes of compliance with MRLs and dietary risk assessment in plant commodities is halauxifen-methyl. The proposed residue definition for halauxifen-methyl for the purposes of compliance with MRLs and dietary risk assessment in animal commodities is 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid (X11449757), expressed as halauxifen-methyl.

Considering the GAP for halauxifen-methyl in wheat and barley in GF-2685 Herbicide, the water dispersible granule formulation containing 100 g/kg each of halauxifen as halauxifen-methyl and cloquintocet-mexyl is a single application of 10 g ai/ha halauxifen as halauxifen-methyl between the 3-leaf (BBCH 13) and flag leaf full emergence (BBCH 39) stages, a harvest withholding period is not required when used as directed, while recommended the grazing withholding period is 2 weeks.

Given that the GAPs for the Australia/New Zealand and USA/Canada trials are essentially the same, the datasets were merged for the purpose of MRL determination. The combined dataset for halauxifen-methyl in wheat, barley and oat grains after treatment at the proposed GAP is <0.003 (20) and <0.01 (45) mg/kg. An MRL of *0.01 mg/kg is therefore proposed for halauxifen-methyl in cereal grains.

In a processing study for wheat, grain from an untreated control plot and a plot treated at 5× the proposed GAP was processed 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.

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 therefore 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 therefore proposed for halauxifen-methyl in forage of cereal grains (green), in conjunction with a 14-day grazing withholding period.

When radiolabelled halauxifen-methyl was applied at 10 g ai/ha (the maximum proposed application rate) in a confined rotational crop study, total radioactive residues were <0.01 mg eq./kg in wheat forage, hay, straw and grain, and immature and mature lettuce and radish roots and tops from crops planted at intervals of 14, 90 and 270 days after application. Residues of halauxifen-methyl are therefore not expected to be found in rotational crops.

The calculated maximum feeding levels for halauxifen-methyl in beef and dairy cattle are 0.37 and 0.17 ppm in feed respectively, or 0.015 and 0.0068 mg/kg bw/day. 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 (residue levels are in 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 (again, residues are in 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 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.

The octanol-water partition coefficient (log10KOW 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 log10KOW 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 log10KOW 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, no MRLs are required to be established in this regard.

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 (well below the maximum level of 0.88 ppm for feeding to ensure no quantifiable residues). 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 an average over a 300 metre distance downwind from the application area (a typical paddock size) gives a mean dry weight pasture concentration over the whole paddock of 0.28 mg/kg for application by plane and 0.32 mg/kg for application by helicopter. These figures 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.

The NEDI was calculated at <1% of the Acceptable Daily Intake for halauxifen-methyl. NESTIs were not calculated, as an Acute Reference Dose has not been established, since pre-systemic exposure to XDE-729 methyl and systemic exposure to XDE-729 acid are unlikely to present an acute hazard to humans after single dose administration. It is concluded that the dietary exposure of halauxifen-methyl is acceptable. No changes to the dietary exposure are expected for cloquintocet-mexyl. No changes to the MRLs for cloquintocet-mexyl are required, and there is no increase to the risk of residues in exported commodities. MRLs for cloquintocet-mexyl in cereals and animal commodities are established at the limit of quantitation.

Based on the residues assessment, the recommended withholding period and statements have been incorporated to the label. APVMA is therefore satisfied that the use of the product in accordance with the label instructions would not be harmful or an undue hazard to the safety of people exposed to residues in food as per section 14(3)(e)(i) & (ii) and has had regard to the residues aspects of section 14(5) of the Agvet Codes. The APVMA is also satisfied that the use of the product in accordance with the required instructions would not unduly prejudice trade and commerce between Australia and places outside Australia as per section 14(3)(e)(iv) of the Agvet Codes, as quantifiable residues of halauxifen-methyl are not expected to be found in cereal grains, nor in the meat, offal, milk or eggs of livestock fed treated forage or fodder. Required entries have been recommended for the MRL Standard.

Data relied on to provide the advice

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71098	S	Ma, M., Smith, K.P., Jackson, U.	A Nature of the Residue Study with [14C]-XR-729 Methyl Applied to Wheat with and without the Safener Cloquintocet Mexyl (Amended Report)	2012	Metabolism and kinetics	Plants	Applicant	
71099	S	Rotondaro, S.L. et al	A Nature of the Residue Study with [14C]-XDE-729 Methyl Applied to Turnips	2012	Metabolism and kinetics	Plants	Applicant	
71101	S	Rotondaro, S.L., Adelfinskaya, Y.A.	A Nature of the Residue Study in the Ruminant with [14C]-XDE-729 Methyl Ester	2011	Metabolism and kinetics	Target animals	Applicant	
71100	S	Rotondaro, S.L., Adelfinskaya, Y.A.	A Nature of the Residue Study in the Laying Hen with [14C]-XDE-729 Methyl Ester	2011	Metabolism and kinetics	Target animals	Applicant	
71083	S	Robaugh, D.A.	Independent Laboratory Validation of Method for the Determination of Residues of XDE-729 Methyl Ester and XDE-729 Acid in Agricultural Commodities and Wheat Processed Products using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection	2012	Residues	Analytical methods	Applicant	
71080	S	Daneva, E., Taeufer, A.	Validation of a multi-residue method for determination of a XDE-729 methyl ester and XDE-729 acid on different matrices of plant origin	2011-10-11	Residues	Analytical methods	Applicant	
71090	S	Langridge, G.	Independent Laboratory Validation of an Analytical Method for the Determination of XDE-729 Methyl Ester and XDE-729 Acid in Animal Matrices	2012	Residues	Analytical methods	Applicant	
71089	S	Ma. M.	Method Validation Study for the Determination of Residues of XDE-729 Methyl Ester and XDE-729 Acid in Bovine and Poultry Tissues using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection.	2012	Residues	Analytical methods	Applicant	
71081	S	Bacher, R.	XDE-729: Independent Laboratory Validation of an Multi-Residue Method for the Determination of XDE-729 Methyl Ester and XDE-729 Acid in Plant Matrices	2011	Residues	Analytical methods	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71084	S	Olberding, E.	Determination of Residues of XDE 729 Methyl Ester and XDE 729 Acid in Agricultural Commodities and Wheat Processed Products using Online Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection	2011	Residues	Analytical methods	Applicant	
71082	S	Ma, M.	Method Validation Study for the Determination of Residues of XDE 729 Methyl Ester and XDE 729 Acid in Agricultural Commodities and Wheat Processed Products using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detec	2012	Residues	Analytical methods	Applicant	
71054	S	Class, T.	Cloquintocet-mexyl: Independent Laboratory Validation of an Analytical Method for the Determination of Cloquintocet-mexyl and Its Acid metabolite in Cereal	2005	Residues	Analytical methods	Applicant	
71053	S	McLean, N.	Method Validation Report for the Determination of Cloquintocet-mexyl and its Acid Metabolite in Wheat Using Enviro-Test Laboratories Method M313.	2006	Residues	Analytical methods	Applicant	
71111	S	Rawle, N.	XDE-729 Livestock Feeding Study: Magnitude of Residue in Milk, Muscle, Fat, Liver and Kidney of Lactating Dairy Cattle	2012	Residues	Animal commodity residues direct application	Applicant	
71102	S	Litzow, D.	Residues of XDE-729 in Wheat Australia 2010	2012	Residues	Crop residues human consumption	Applicant	
71103	S	Montagna, M.	Residues of XDE-729 in Wheat Australia 2011	2012	Residues	Crop residues human consumption	Applicant	
71110	S	Korpalski, S.J.	Magnitude and Decline of the Residues of XDE-729 Following Spring Application of GF-2685 to Barley	2012	Residues	Crop residues human consumption	Applicant	
71113	S	Rotondaro, S.L.	A Confined Rotational Crop Study with [14C]-XDE-729 Methyl Ester	2011	Residues	Crop residues human consumption	Applicant	
71109	S	Korpalski, S.J.	Magnitude and Decline of the Residues of XDE-729 Following Spring Application of GF-2685 to Barley	2011	Residues	Crop residues human consumption	Applicant	
71108	S	Montagna, M.	Residues of XDE-729 in Barley Australia 2011	2012	Residues	Crop residues human consumption	Applicant	
71107	S	Litzow, D.	Residues of XDE-729 in Barley Australia 2010	2012	Residues	Crop residues human consumption	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71106	S	Korpalski, S.J.	Magnitude of XDE-729 Residues Following Sping Applications of GF-2685 to Wheat	2012	Residues	Crop residues human consumption	Applicant	
71112	S	Korpalski, S.J.	Magnitude of the Residues of XDE-729 in Wheat Process Fractions Following Spring Application of GF-2685 to Wheat	2012	Residues	Crop residues human consumption	Applicant	
71104	S	Litzow, D.	Residues of XDE-729 in Wheat New Zealand 2011	2012	Residues	Crop residues human consumption	Applicant	
71105	S	Korpalski, S.J.	Magnitude and Decline of the Residues of XDE-729 Following Spring Application of GF-2685 to Wheat	2011	Residues	Crop residues human consumption	Applicant	
71057	S	Litzow, D.	Residues of XDE-729 in Oats Australia 2010	2012	Residues	Crop residues livestock feed	Applicant	
71058	S	Montagna, M.	Residues of XDE-729 in Oats Australia 2011	2012	Residues	Crop residues livestock feed	Applicant	
71055	S	Class, T.	Cloquintocet-Mexyl and Its Acid Metabolite: Freezer Storage Stability in Plant Materials and in Soil.	2007	Residues	Fate - storage, processing and cooking	Applicant	
71095	S	Devine, H.C.	X11393728 (XDE-729 methyl) and X11393729 (XDE-729): Residue Stability Study in Crops under Freezer Storage Conditions	2012	Residues	Fate - storage, processing and cooking	Applicant	
71056	S	Langridge, G.	Frozen Storage Stability of Residues of XDE-729 Methyl Ester, XDE-729 Acid and X-11449757 in Animal Matrices - Five Months Stability Data for XDE-729 Methyl Ester and XDE-729 Acid and One Month Stability Data for X11449757 INTERIM REPORT	2012	Residues	Fate - storage, processing and cooking	Applicant	
71096	S	Devine, H.C.	Cloquintocet-mexyl and Cloquintocet-acid: Residue Stability Study in Crops Under Freeszer Storage Conditions - INTERIM REPORT NUMBER 1: Eleven Months Stability Data	2012	Residues	Fate - storage, processing and cooking	Applicant	

State/External Efficacy Reviewer

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 over 2009-11. The 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 species 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 100g/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 was observed 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 were applied as recommended on the label with an adjuvant/wetter 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 (100g/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. 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.

The efficacy reviewer concluded that GF- 2685 Herbicide achieved 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 reviewer supported the proposed registration of GF-2685 Herbicide for the control of a range of broadleaf weeds in wheat and barley crops as per the label claims.

Considering the efficacy reviewer’s advice, the APVMA is satisfied that the use of the product would be effective and safe when used in accordance with the proposed label instructions.

Data relied on to provide the advice

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71075	S	Nott, P.	Individual Study Reports of Efficacy Trials Conducted For the Proposed Uses of GF-2685 on Wheat and Barley Crops in Australia.	2012	Efficacy and safety	Efficacy	Applicant	
71190	S	Gifford, J.M. et al	Rainfastness XDE-729 formulations , GF-2685 or GF-2687 in combination with Turbocharge and GF-2688 compared to a commercial formulation Primus (EF-1343).	2012	Efficacy and safety	Other information	Applicant	
71191	S	Satchivi, N.M. et al	Fate of XDE-729 Methyl Ester Applied to Cereal Crops: Effects of Straw Residues on Legume and Vegetable Crops	2012	Efficacy and safety	Other information	Applicant	
71078	S	Nott, P.	Individual Study Reports of Plantback Trials Conducted For the Proposed Uses of GF-2685 on Wheat and Barley Crops in Australia.	2012	Efficacy and safety	Phytotoxicity and crop safety	Applicant	
71077	S	Elias,N., Coates, R., Nott, P.	GF-2685 and GF-2687 recropping intervals to cereals and canola, Australia 2011	2012	Efficacy and safety	Phytotoxicity and crop safety	Applicant	
71076	S	Nott, P.	Individual Study Reports of Selectivity Trials Conducted For the Proposed Uses of GF-2685 on Wheat and Barley Crops in Australia.	2012	Efficacy and safety	Phytotoxicity and crop safety	Applicant	

** S = Data submitted with the application; I = Data inherited (that is, referenced) from another application*