



ADVICE SUMMARY
ACTIVE CONSTITUENT APPLICATION

Active Constituent name: HALAUXIFEN-METHYL
Applicant: DOW AGROSCIENCES AUSTRALIA LIMITED
Active Constituent number: 68243
Application number: 57828

Purpose of Application and Description of Use: Approval of Halauxifen-methyl for use in agricultural chemical products.

Regulatory Decision:

To grant the application to approve the active constituent subject to the following conditions:

Standard Conditions of Registration/Approval

1. Agricultural Active Constituents must meet Quality Assurance Requirements

For full conditions, refer to Standard Conditions for Applications on the APVMA website.

For the Guideline to the Type of Information the APVMA will routinely publish in relation to applications see the Advice Summaries page on the APVMA website.

Non-Standard Conditions of Registration/Approval

N/A

ADVICE

Australian Government Department of Health and Ageing, Office of Chemical Safety

The Office of Chemical Safety (OCS) has completed a toxicological evaluation of halauxifen-methyl.

An Acceptable Daily Intake (ADI) of 0.1 mg/kg bw/d has been set, based on a No-Observed Effect Level (NOEL) 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 acute reference dose (ARfD) is not proposed for halauxifen-methyl, as it is considered unlikely to present an acute hazard to humans after single dose administration based on the use patterns proposed.

Halauxifen-methyl is not currently in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). The delegate to the Secretary of the Department of Health has made a delegate only decision on halauxifen 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 (SUSMP), along with an implementation date of 1st October 2014.

The OCS has indicated that there are no objections on toxicological grounds to the approval of the active constituent Halauxifen-methyl.

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.
71241	S	Durando, J.	Acute Dermal Toxicity Study In Rats	2009	Toxicology	Acute dermal studies, active	Applicant	
71242	S	Durando, J.	Acute Dermal Toxicity Study in Rats	2011	Toxicology	Acute dermal studies, active	Applicant	
71259	S	Stebbins, K.E. et al	XDE-729: 28-Day Dermal Toxicity Study in F344/DuCrI Rats	2010	Toxicology	Acute dermal studies, active	Applicant	
71246	S	Durando, J.	Primary Eye Irritation Study in Rabbits	2010	Toxicology	Acute eye irritation studies, active	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71247	S	Durando, J.	Primary Eye Irritation Study in Rabbits	2011	Toxicology	Acute eye irritation Sstudies, active	Applicant	
71243	S	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	Applicant	
71240	S	Durando, J.	Acute Oral Toxicity Up and Down Procedure in Rats	2011	Toxicology	Acute oral studies, active	Applicant	
71244	S	Durando, J.	Primary skin irritation study in rabbits	2009	Toxicology	Acute skin irritation studies, active	Applicant	
71245	S	Durando, J.	Primary skin irritation study in rabbits	2011	Toxicology	Acute skin irritation studies, active	Applicant	
71249	S	Boverhof, D.R., Sosinski, L.K.	XDE-729 methyl: Local Lymph Node Assay in CBA/J Mice	2011	Toxicology	Acute skin sensitisation studies, active	Applicant	
71248	S	Boverhof, D.R., Sosinski, L.K.	XR-729: Local Lymph Node Assay in CBA/J Mice	2011	Toxicology	Acute skin sensitisation studies, active	Applicant	
71271	S	Thomas, J. et al	XDE-729: 18-Month Dietary Oncogenicity Study in CrI:CD1(ICR) Mice	2012	Toxicology	Chronic/carcinogenicity studies	Applicant	
71270	S	Stebbins, K.E. et al	XDE-729: Two-Year Chronic Toxicity/Oncogenicity Study in F344/DuCrI Rats	2012	Toxicology	Chronic/carcinogenicity studies	Applicant	
71258	S	Heward, J.	XDE-729: 1 Year Oral (Dietary) Toxicity Study in Beagle Dogs	2012	Toxicology	Chronic/carcinogenicity studies	Applicant	
71285	S	Ellis-Hutchings, R.G. et al	XDE-729: Dietary Developmental Toxicity Study in New Zealand White Rabbits	2011	Toxicology	Developmental (teratology) studies	Applicant	
71284	S	Ellis-Hutchings, R.G. et al	XDE-729: Dietary Developmental Toxicity Probe Study in New Zealand White Rabbits	2011	Toxicology	Developmental (teratology) studies	Applicant	
71283	S	Ellis-Hutchings, R.G. et al	XDE-729 methyl: Dietary Developmental Toxicity Study in CrI:CD (SD) Rats	2012	Toxicology	Developmental (teratology) studies	Applicant	
71287	S	Ellis-Hutchings, R.G. et al	XDE-729 Methyl: Developmental Toxicity Study in New Zealand White Rabbits	2012	Toxicology	Developmental (teratology) studies	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71286	S	Ellis-Hutchings, R.G. et al	XDE-729 Methyl: Developmental Toxicity Probe Study in New Zealand White Rabbits	2012	Toxicology	Developmental (teratology) studies	Applicant	
71282	S	Ellis-Hutchings, R.G. et al	XDE-729 methyl: Dietary Developmental Toxicity Probe Study in Crl:CD (SD) Rats	2012	Toxicology	Developmental (teratology) studies	Applicant	
71281	S	Ellis-Hutchings, R.G., Marshall, V.A.	XDE-729: Dietary Developmental Toxicity Study in Crl:CD (SD) Rats	2010	Toxicology	Developmental (teratology) studies	Applicant	
71261	S	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	Applicant	
71262	S	Nagane, R.M.	Bacterial Reverse Mutation Test of XDE-729 Methyl TGAI Using Salmonella Typhimurium	2012	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71263	S	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	Applicant	
71264	S	Schisler, M.R.	Evaluation of XDE-729 methyl in an in vitro chromosomal aberration assay utilizing rat lymphocytes	2012	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71265	S	Nagane, R.M.	In vitro Mammalian Chromosome Aberration Test of XDE-729 Methyl TGAI in Human Peripheral Blood Lymphocytes	2012	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71266	S	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	Applicant	
71267	S	Schisler, M.R	Evaluatiou of XDE-729 Methyl in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay	2011	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71268	S	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	Applicant	
71269	S	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	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71290	S	Nagane, R.M.	Bacterial Reverse Mutation Test of X11449757 using Salmonella typhimurium	2012	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71291	S	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 X11449757	2012	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71272	S	LeBaron, M.J. et al	Hepatic Gene Expression and Biomarker Analyses in Male F344/DuCrI Rats Administered XDE-729 or XDE-729 Methyl for Seven Days	2012	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71292	S	Nagane, R.M.	In Vitro Mammalian Chromosome Aberration Test of X11449757 in Human Peripheral Blood Lymphocytes	2012	Toxicology	Genotoxicity (mutagenicity) studies	Applicant	
71260	S	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	Applicant	
71294	S	Lu, H.	XDE-729 Methyl Toxicology Overview	2012	Toxicology	Other information	Applicant	
71279	S	Carney, E. W. et al	XDE-729: A Reproduction/Developmental Toxicity Probe Study in CrI:CD(SD) Rats	2010	Toxicology	Reproduction studies	Applicant	
71280	S	Rasoulpour, R.J. et al	XDE-729: Two Generation Dietary Reproductive Toxicity Study in CRL:CD (SD) Rats	2011	Toxicology	Reproduction studies	Applicant	
71250	S	Yano, B. L. et al	XR-729: 28-day Dietary Toxicity Study in F344/DUCRL Rats	2009	Toxicology	Short-term studies	Applicant	
71251	S	Stebbins, K.E., Marshall, V.A., McCoy, A.T.	XDE-729 Methyl: 28-day Dietary Toxicity Study in F344/DuCrI Rats	2011	Toxicology	Short-term studies	Applicant	
71253	S	Popke, E.J.	XR-729: Palatability Probe and 28-Day Dietary Toxicity Study in Beagle Dogs	2010	Toxicology	Short-term studies	Applicant	
71252	S	Thomas, J. et al	XR-729: 28-Day Dietary Toxicity Study in CrI:CD1(ICR) Mice	2009	Toxicology	Short-term studies	Applicant	
71273	S	Sura, R. et al	XDE-729 Methyl: 7Day Dietary Toxicity Probe Study on CrI:CD1 ICR Mice	2012	Toxicology	Short-term studies	Applicant	
71278	S	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	Applicant	

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
71275	S	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	Applicant	
71277	S	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	Applicant	
71276	S	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	Applicant	
71288	S	Marty, M. S., Andrus, A. K. and Sura, R.	XDE-729: Acute Neurotoxicity in F344/DuCrI Rats	2010	Toxicology	Studies of other special effects	Applicant	
71289	S	Marty, M. S., Andrus, A. K. and Sura, R.	XDE-729: 90-Day Dietary Neurotoxicity Study in F344/DuCrI Rats	2011	Toxicology	Studies of other special effects	Applicant	
71293	S	Boverhof, D.R. et al	XDE-729 Methyl: Assessment of Immunotoxic Potential Using the Sheep Red Blood Cell Assay after 28-Day Dietary Exposure to Female F344/DuCrI Rats	2012	Toxicology	Studies of other special effects	Applicant	
71274	S	Boverhof, D.R. et al	XDE-729 Methyl: Evaluation of Molecular and Cellular Changes in the Livers of Male F344/DuCrI Rats after a Four Week Dietary Exposure and a Four Day or 28 Day Recovery Period.	2012	Toxicology	Studies of other special effects	Applicant	
71256	S	Thomas, J. et al	XDE-729: 90-Day Dietary Toxicity Study in CrI:CD1(ICR) Mice	2010	Toxicology	Sub-chronic studies	Applicant	
71257	S	Heward, J.K.	XDE-729: A 90-Day Oral (Dietary) Toxicity Study in Beagle Dogs	2011	Toxicology	Sub-chronic studies	Applicant	
71255	S	Stebins, K.E. et al	XDE-729 Methyl: 90-Day Dietary Toxicity Study in DuCrI/F344 Rats	2012	Toxicology	Sub-chronic studies	Applicant	
71254	S	Yano, B.L. et al	XDE-729: 90-Day Dietary Toxicity Study in F344/DUCRL Rats	2010	Toxicology	Sub-chronic studies	Applicant	

* S = Data submitted with the application