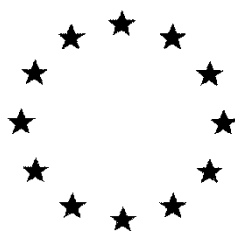


European Commission



**Draft Assessment Report prepared according to the Commission
Regulation (EU) N° 1107/2009**

XDE-729 Methyl (Halauxifen-methyl) Volume 1

**Rapporteur Member State: United Kingdom
Co-Rapporteur Member State: France**

Version History

When	What
2013-12-19	Initial DAR

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LEVEL 1

**XDE-729 Methyl
(Halauxifen-methyl)**

**LEVEL 1: STATEMENT OF THE SUBJECT MATTER AND PURPOSE FOR WHICH
THE DRAFT ASSESSMENT REPORT WAS PREPARED**

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1.1 Purpose for which the draft assessment report was prepared

This draft assessment report on XDE-729 Methyl (halauxifen-methyl) has been prepared for submission to the European Commission to enable a decision to be made on the first approval of XDE-729 Methyl as a new active substance under Regulation (EC) No. 1107/2009. The UK Chemicals Regulation Directorate, HSE, is the Rapporteur Member State and France is the co-rapporteur.

1.2 Summary and assessment of information relating to the collective provision of the dossier

Not relevant as XDE-729 Methyl is a new active substance and Dow AgroSciences is the sole applicant.

1.3 Identity of the active substance

1.3.1 Name and address of applicant(s) for approval of the active substance (Annex IIA 1.1)

Central Address	Dow AgroSciences [REDACTED] [REDACTED] [REDACTED] [REDACTED]
Telephone	[REDACTED]
Facsimile	[REDACTED]
Contact	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
Member State Address	Dow AgroSciences Limited [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
Telephone	[REDACTED]
Facsimile	[REDACTED]
Contact	[REDACTED])

1.3.2 Common name and synonyms (IIA 1.3)

ISO common name (proposed)	Halauxifen-methyl
Synonyms	XDE-729 methyl, XDE-729 Me, XDE-729-Me, XR-729 methyl, XDE-729 ME, XR-728, XD-729, XDE-729 ME PAI, XD-728, XR-729 X11393728

1.3.3 Chemical name (IIA 1.4)

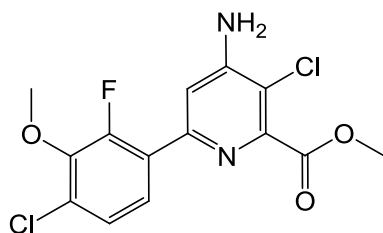
IUPAC	Methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate
IUPAC – using older software	4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylic acid methyl ester
CA	2-pyridinecarboxylic acid, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-, methyl ester

1.3.4 Manufacturer's development code number (IIA 1.5)

Code	Period of use/comments
X11393728	-
XDE-729 methyl	Used from 2009 to 2011 for the active substance
XDE-729 ME	Used from 2009 to 2011 for the active substance
XD-728	-
XR-728	-
GF-2573	Used from 2008 to current for the EC formulated product.

1.3.5 CAS, EEC and CIPAC numbers (IIA 1.6)

CAS:	943831-98-9
EECS:	Not available
ELINCS:	Not available
CIPAC:	Not available

1.3.6 Molecular and structural formulae, molecular mass (IIA 1.7)

Molecular Formula :

 $C_{14}H_{13}Cl_2FN_2O_3$

Molecular Weight :

347.17

1.3.7 Manufacturer(s) of the active substance (IIA 1.2)

Confidential information (see Volume 4).

1.3.8 Method(s) of manufacture (IIA 1.8)

Confidential information (see Volume 4).

1.3.9 Specification of purity of the active substance (IIA 1.9)

XDE-729 methyl has a minimum purity of 93.0% (930 g/kg). This is based on pilot scale material.

1.3.10 Identity of isomers, impurities and additives (IIA 1.10)

Confidential information (see Volume 4).

1.3.11 Analytical profile of batches (IIA 1.11)

Confidential information (see Volume 4).

1.4 Identity of the plant protection product**1.4.1 Current, former and proposed trade names and development code numbers (IIIA 1.3)**

Trade name not available at the time of writing the DAR; however, the code used for the EC (Emulsion Concentrate) formulation is GF-2573 in the present dossier.

1.4.2 Manufacturer(s) of the plant protection product (IIIA 1.2)

Manufacturer(s) of the preparation

Address	[REDACTED]
Telephone	[REDACTED]
Facsimile	[REDACTED]
Contact	[REDACTED]

Alternate Supplier for the preparation

Address	[REDACTED]
Telephone	[REDACTED]
Facsimile	[REDACTED]
Contact	[REDACTED]

1.4.3 Type of the preparation and code (IIIA 1.5)

EC (Emulsion Concentrate)

1.4.4 Function (IIA 3.1, IIIA 1.6)

Herbicide

1.4.5 Composition of the preparation (IIIA 1.4)

Confidential information (see Volume 4).

1.5 Uses of the plant protection product**1.5.1 Field of use (IIA 3.3, IIIA 3.1)**

Agriculture

1.5.2 Effects on harmful organisms (IIA 3.2; IIIA 3.2)

XDE-729 methyl acts as a post-emergence systemic herbicide for the control of a range of broad leaved weeds frequently damaging cereal crops in the European Union. It has the flexibility to be used from early autumn through late spring in winter cereals.

1.5.3 Summary of intended uses (IIA 3.4; IIIA 3.3, 3.4, 3.5, 3.6, 3.7, 3.9)

XDE-729 methyl is a new active substance belonging to a new family of 6-arylpicolinate herbicides. XDE-729 methyl is a member of the pyridine-carboxylic family of herbicidal auxins (HRAC Group O).

XDE-729 methyl is intended for the control of a range of broad-leaved weed species post-emergence at a maximum dose of 7.5 g a.s/ha. It is proposed for use in winter and spring cereals, from early autumn through late spring. It provides a phenotypic response similar to the natural auxins and synthetic auxin herbicides.

The information supplied on both the active and product adequately addresses data on application.

1.5.3.1 Details of intended uses (IIIA 3.3, IIA 3.4)

See Table 1.1 below:

Table 1.1: Summary of EU intended uses

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number min max	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		
Winter cereals (soft wheat, durum wheat, barley, spelt, rye, triticale)	EU	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 10 to 29 and BBCH 13 - 45	1-2	0.00196-0.00782 followed by 0.00156 – 0.00625	100-400	0.00782 followed by 0.00625		The applications are made in autumn only (7.82 g/ha), or in spring only (6.25 g/ha) or in both autumn and spring (7.82 + 6.25 g/ha). Autumn applications are from BBCH 10 to 29. Spring applications are from BBCH 13 to 45.
Spring cereals (wheat, barley, durum wheat, rye)	EU	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 13 to 45	1	0.00156 – 0.00625	100-400	0.00625		The application is made in spring only, from BBCH 13 to 45.

Summary of intended uses on Zonal Basis

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number min max	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		

Northern Zone

Winter cereals (soft wheat, barley, rye, triticale)	Northern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 10 to 29 (Sep 1st- Dec 31st) and BBCH 13 to 45 (March 1 st - Jun 20th)	1-2	0.00196-0.00782 followed by 0.00156 – 0.00625	100-400	0.00782 followed by 0.00625		The applications are made in autumn only (7.82 g/ha), or in spring only (6.25 g/ha) or in both autumn and spring (7.82 + 6.25 g/ha). Autumn applications are from BBCH 10 to 29, from Sept 1st to Dec 31st. Spring applications are from BBCH 13 to 45, from March 1st to June 20th.
Spring cereals (wheat, barley)	Northern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 13 to 45 (March 1 st – Jun 20th)	1	0.00156 – 0.00625	100-400	0.00625		The application is made in spring only, from BBCH 13 to 45, from March 1st to June 20th

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number min max	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		

Central Zone

Winter cereals (soft wheat, durum wheat, barley, spelt, rye, triticale)	Central Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 10 to 29 (Sep 1st - Dec 31st) and BBCH 13 to 45 (Jan 1st - Jun 30th)	1-2	0.00196-0.00782 followed by 0.00156 – 0.00625	100-400	0.00782 followed by 0.00625		The applications are made in autumn only (7.82 g/ha), or in spring only (6.25 g/ha) or in both autumn and spring (7.82+6.25 g/ha). Autumn applications are from BBCH 10 to 29, from Sept 1st to Dec 31st. Spring applications are from BBCH 13 to 45, from January 1st to June 30th
Spring cereals (wheat, barley, durum wheat, rye)	Central Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 13 to 45 (Feb 1st - Jun 30th)		0.00156 – 0.00625	100-400	0.00625		The application is made in spring only, from BBCH 13 to 45, from February 1st to June 30th

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number min max	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		

Southern Zone

Winter cereals (soft wheat, durum wheat, barley, spelt, rye, triticale)	Southern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 10 to 29 (Sep 1st- Dec 31st) and BBCH 13 to 45 (Jan 1st - May 31 st)	1-2	0.00196-0.00782 followed by 0.00156 – 0.00625	100-400	0.00782 followed by 0.00625		The applications are made in autumn only (7.82 g/ha), or in spring only (6.25 g/ha) or in both autumn and spring (7.82+6.25 g/ha). Autumn applications are from BBCH 10 to 29, from Sept 1st to Dec 31st. Spring applications are from BBCH 13 to 45, from January 1st to May 31 st
Spring cereals (wheat, barley, durum wheat, rye)	Southern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 13 to 45 (Feb 1st- May 31 st)	1	0.00156 – 0.00625	100-400	0.00625		The application is made in spring only, from BBCH 13 to 45, from February 1st to May 31 st

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (e.g. fumigation of a structure)

(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)

(c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds

(d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989

(f) All abbreviations used must be explained

(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench

(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated

(i) g/kg or g/l

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(l) PHI - minimum pre-harvest interval

(m) Remarks may include: Extent of use/economic importance/restrictions

1.5.3.2 Application rate (IIIA 3.4)

The applications are made in autumn only (7.82 g/ha), or in spring only (6.25 g/ha) or in both autumn and spring (7.82+6.25 g/ha).

1.5.3.3 Concentration of active substance in material used (IIIA 3.5)

All recommended applications involve dilution in water as the carrier or dilutant. The recommended application volume is 100 to 400 L water/ha (i.e. maximum concentration = 0.00782 and minimum = 0.00196 kg as/hl).

See table B.3.1 above for further details.

1.5.3.4 Method of application (IIIA 3.6)

GF-2573 can be applied through all conventional sprayers including tractor mounted or self propelled hydraulic sprayers.

1.5.3.5 Number and timing of applications and duration of protection (IIIA 3.7)

The applications are made in autumn only (7.82 g/ha), or in spring only (6.25 g/ha) or in both autumn and spring (7.82+6.25 g/ha). Autumn applications are from BBCH 10 to 29. Spring applications are from BBCH 13 to 45.

See Summary of intended uses (table 1.1) for more details.

The applicant has stated:

XDE-729 methyl will provide season long control of sensitive weed species present at the time of application. It will not control sensitive weed species which emerge post application because XDE-729 methyl does not provide residual control.

1.5.3.6 Necessary waiting period or other precautions to avoid phytotoxic effects on succeeding crops (IIIA 3.8)

- 1) Minimum waiting periods or other precautions between last application and sowing or planting succeeding crops

The applicant has stated:

Autumn applications of XDE-729 methyl :

In most of the cases, XDE-729 methyl was applied in November and succeeding crops were sown in March-April after plough (4-5 months after treatment).

XDE-729 methyl was perfectly safe to all tested crops, whatever the local conditions.

Thus, after an autumn application of XDE-729 methyl, all tested crops (spring barley, spring wheat, spring oil seed rape, maize, sunflower, ryegrass, field beans or peas) can be safely sown after ploughing in spring.

Spring applications of XDE-729 methyl :

XDE-729 methyl was applied either in March or in April. Succeeding crops were sown 1 or 2 months later. Two soil cultivation practices were tested: either plough or minimum tillage before sowing the succeeding crops.

Results which have been achieved specify that after a spring application of XDE-729 methyl, it is possible to sow :

- 1 month after application (whatever the soil cultivation practice):
 - Spring wheat
 - Spring barley
 - Maize
 - Faba beans
 - Spring oil seed rape
- 2 months after application (whatever the soil cultivation practice) :
 - Sunflower

Conclusion: In case of unexpected crop failure, XDE-729 persistence in soil is short enough to allow farmers sowing a wide range of frequent crops, after either autumn or spring applications, whatever the soil cultivation practices (plough or minimum tillage).

2) Limitations on choice of succeeding crops

The applicant has indicated that following an autumn application there will be no restrictions in the choice of succeeding crops. However, following a spring application the following restrictions will apply

- 1 month after application (whatever the soil cultivation practice):
 - Spring wheat
 - Spring barley
 - Maize
 - Faba beans
 - Spring oil seed rape
- 2 months after application (whatever the soil cultivation practice) :
 - Sunflower

3) Description of damage to rotational crops

The applicant has indicated that symptoms of herbicide damage include: cessation of growth, epinasty, leaf cupping, chlorosis, swelling/thickening of stems and distortion of the meristems and in very severe cases plant death.

1.5.3.7 Proposed instructions for use (IIIA 3.9)

See Table 1.1 above. The applicant has submitted a draft label for the proposed use of representative formulation 'GF-2573' see Volume 3, Appendix 2.

1.5.4 Information on authorisations in EU Member States (IIIA 12.1)

XDE-729 Methyl is a new active substance in the EU. There are currently no registered uses.

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LEVEL 2

XDE-729 Methyl (Halauxifen-methyl)

**LEVEL 2: REASONED STATEMENT OF THE OVERALL CONCLUSIONS
DRAWN BY THE RAPPORTEUR MEMBER STATE**

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

2.1.1 Identity

XDE-729 methyl is an ester form of XDE-729 acid. XDE-729 (Halauxifen-methyl) is a new herbicide. 'GF-2573' is the plant protection product and is an Emulsion Concentrate (EC) containing 7.8 g/L of the active ingredient XDE-729 methyl (7.5 g acid equivalent (a.s) /L). The formulation also contains a herbicide safener, cloquintocet-mexyl, at a nominal concentration of 7.5 g a.s/L.

The proposed technical specification based on pilot plant production is supported by the results of the analysis of the five analytical batches. Acceptable data have been submitted for the identity of the active substance and plant protection product for the purposes of authorisation. Following scale-up from pilot plant to full scale manufacture new 5-batch analysis supporting the commercial scale technical specification must be submitted. In addition the toxicological significance of any changes in the impurity profile must be addressed. In the case of XDE-729 Methyl, the RMS was unable to conclude that material of the proposed technical specification is toxicologically equivalent to the material used in the XDE-729 Methyl toxicity studies.

The RMS proposes that the equivalence of the technical specification to the material used in the toxicity testing is addressed when the final technical specification of XDE-729 Methyl has been determined, because it is possible that the quantity of an impurity present in the 5-batch analysis, but not in the batches used for the toxicological studies, may be lower in the final specification, such that toxicological equivalence is no longer an issue.

See Volume 4 for further details regarding the specific concerns and data requirements for future submission of batch analysis for full scale manufacture.

2.1.2 Physical and chemical properties

XDE-729 is a white solid with a mild odour. It has a relative density D_4^{20} of 1.5057. The melting point is 145.5°C, with decomposition before boiling. The temperature of decomposition or sublimation is 221.06°C. ^1H NMR, ^{13}C NMR, TSI+/TSI- MS and IR spectra support the structure of XDE-729. XDE-729 is not explosive, flammable, auto-flammable or oxidising. XDE-729 is very slightly volatile with a vapour pressure of 1.5×10^{-8} Pa at 25°C. Aqueous solubility is not pH dependent with XDE-729 being slightly soluble at pH 5 (1.66 mg/L), pH 7 (1.67 mg/L) and at pH 9 (1.69 mg/L). XDE-729 is very slightly volatile in solution at pH 5, pH 7 and pH 9 (Henry's law constant at 25°C is 1.23×10^{-6} Pa.m³.mol⁻¹, 1.22×10^{-6} Pa.m³.mol⁻¹, 1.20×10^{-6} Pa.m³.mol⁻¹). The pKa is 2.84 ± 0.04 at 20°C. Thus volatilisation is not expected to contribute significantly to the dissipation of XDE-729 in the environment. The hydrolysis half-life of XDE-729 is 81 days in solution at pH 4 at 25°C, 155 days at pH 7 (25°C) and 3 days at pH 9 (25°C). Therefore XDE-729 is classified as slightly hydrolysing at pH 4 and 7 and readily hydrolysing at pH 9. There is significant absorbance >290 nm in the UV-Vis spectrum for XDE-729 when in solution at pH < 2, therefore at low pH XDE-729 is photolytically labile. At pH 7 and pH > 10, there is no significant absorbance >290nm in the UV-vis spectrum, therefore at higher pH XDE-729 is photolytically

stable. The estimated atmospheric half-life for XDE-729 is estimated to be 25.87 hours. XDE-729 is very slightly soluble in n-heptane (0.0361 mg/L), slightly soluble in n-octanol and xylene (9.83 mg/L, 9.13 mg/L) and moderately soluble in ethyl acetate, 1,2-dichloromethaneacetone, acetone and methanol (129 mg/L, 65.9 mg/L, >250 mg/L and 38.1 mg/L). The n-octanol/water partition coefficient is not pH dependent ($\text{Log}_{10}P_{\text{OW}} = 3.75$ at pH 5, $\text{Log}_{10}P_{\text{OW}} = 3.76$ at pH 7 and $\text{Log}_{10}P_{\text{OW}} = 3.92$ at pH 9). The data suggest a potential to be fat soluble. The surface tension of a 90% aqueous solution of XDE-729 at 20°C is 72.5 mN.m⁻¹.

The representative plant protection product for XDE-729 is 'GF-2573'. 'GF-2573' is an Emulsion Concentrate (EC) formulation containing 7.817g active substance XDE-729 methyl/L and 7.5 g cloquintocet-mexyl/L. 'GF-2573' is a yellow liquid (25.5°C) with a solvent odour, it is not classified for physico-chemical properties. When analysed by HPLC, the active substance content in the formulation was within specification. The pH of a 1% dispersion in water is pH 5.3. 'GF-2573' has a relative density of 0.905. Surface tension for a 0.27% v/v dilution at 20°C was 33.0 mN/m and for a 1.25% v/v dilution at 20°C was 29.5 mN/m. Viscosity at 40°C was 4.22 mPa.s. A written statement was provided stating that the hydrocarbon content does not exceed 10%. This statement is confirmed by reference to the formulation details in document J (see also Volume 4s). The product does not require further consideration as an aspiration hazard. Levels of persistent foam and emulsion characteristics are within acceptable limits. The active substance content and all physicochemical properties were acceptably retained after accelerated storage (18 days at 54°C) and 12 months storage at ambient temperature; a 2-year shelf life study is ongoing, acceptable retention of properties were demonstrated following cold temperature storage.

Two studies were submitted to address effectiveness of tank cleaning procedures as part of the submission. These studies have not been evaluated as part of the consideration for authorisation of XDE-729 methyl, they are for consideration by efficacy experts during evaluation of the product at member state level. It is noted however, that the notifier concludes that there is potential for low levels of crop injury to subsequent crops, and therefore as a precautionary approach, the following label text has been suggested for GF-2573 by the notifier:

TANK CLEANING

XDE-729 methyl (GF-2573) is active to a range of broad-leaved crop species. To avoid subsequent injury to crops other than cereals (wheat, durum wheat, spelt, barley, rye, triticale), all spraying equipment must be thoroughly cleaned both inside and out.

The use of a proprietary cleaner such All Clear Extra at 0.5 % v/v or bleach containing 5 % hypochlorite is advised where sensitive crops are likely to be sprayed following use of XDE-729 methyl containing products.

2.1.3 Details of uses, summary of efficacy and further information

XDE-729 methyl is a new active substance belonging to a new family of 6-arylpicolinate herbicides. XDE-729 methyl is a member of the pyridine-carboxylic family of herbicidal auxins (HRAC Group O).

XDE-729 methyl is intended for the control of a range of broad-leaved weed species post-emergence at a maximum dose of 7.5 g a.s/ha. It is proposed for use in winter and spring cereals, from early autumn through late spring. It provides a phenotypic response similar to the natural auxins and synthetic auxin herbicides.

For approval of an active substance 'a plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements: a) it shall be sufficiently effective and c) it shall not have any unacceptable effects on plants or plant products'. The applicant has addressed this requirement.

The information supplied on both the active and product adequately addresses data on application.

2.1.4 Classification and labelling

2.1.4.1 Active substance classification and labelling requirements

Physical and chemical properties

None

Classification of the active substance on the basis of toxicological properties

Classification proposal according to Directive 67/548/EEC

Hazard symbol: None

Indication of danger: None

Risk phrases: None

Safety phrases: None

Justification: The active substance does not meet the criteria for classification on the basis of its toxicological properties under Directive 67/548/EEC.

Classification proposal according to Regulation 1272/2008

Pictogram: None

Signal word: None

Hazard class: None

Hazard statements: None

Justification: The active substance does not meet the criteria for classification on the basis of its toxicological properties under Regulation 1272/2008.

Classification of the active substance for environmental effects**Provisional classification of the active substance for environmental effects according to 67/548/EEC**

XDE-729 methyl (67/548/EEC)		
Hazard symbol:		Dangerous for the environment
Risk phrases:	R 50/53	Very toxic to aquatic organisms, may cause long term adverse effects in the aquatic environment
Safety phrases:	S60	This material and its container must be disposed of as hazardous waste
	S61	Avoid release to the environment. Refer to special instructions/safety data sheets
	S59	Refer to manufacturer/supplier for information on recovery/recycling
<u>Justification for the proposals:</u>		
Risk phrases:	R 50	<i>Myriophyllum spicatum</i> 14 d E ₁ C ₅₀ 0.000393 mg a.s./L (< 1 mg/L)
	R53	Not readily biodegradable
Safety phrases:	S60/61	Recommended for substances that may cause effects in the environment
	S59	Recommended for all dangerous substances recommended for recovery/recycling but <u>obligatory</u> for substances classified as dangerous for the ozone layer (R59)

Provisional hazard classification of the active substance for environmental effects according to Regulation (EC) 1272/2008

Pictogram	GHS09
Signal word	Warning
Hazard statements	H400/H410: Very toxic to aquatic life/Very toxic to aquatic life with long lasting effects (acute/chronic category 1).
M-factor	1000 acute; 1000 chronic
Precautionary statements	P273 Avoid release to the environment P391 Collect spillage P501 Dispose of contents/ container to ... (in accordance with local/ regional/ national/ international regulation (to be specified))

Justification for classification according to Regulation (EC) 1272/2008

H410	Required as XDE-729 methyl is an 'acute category 1' and 'chronic category 1' substance, as defined by: i) <i>Myrio-hyllum spicatum</i> 14 d ErC_{50} 0.000393 mg a.s./L ii) <i>Myrio-hyllum spicatum</i> 14 d NOEC <0.0000617 mg a.s./L iii) substance not 'rapidly biodegradable'(cross ref fate section 8.4.3)
M-factor	i) <i>Myrio-hyllum spicatum</i> 14 d ErC_{50} 0.000393 mg a.s./L (> 0.0001 to $\leq$ 0.001 mg/L) ii) <i>Myrio-hyllum spicatum</i> 14 d NOEC <0.0000617 mg a.s./L (> 0.00001 to $\leq$ 0.0001 mg/L, not rapidly biodegradable)
GHS09 Pictogram	Required for 'acute category 1' and 'chronic category 1' substance
Signal word 'Warning'	Required for 'acute category 1' and 'chronic category 1' substance
P273, P 391, P 501	Required for 'acute category 1' and 'chronic category 1' substance

2.1.4.2 Preparation classification and labelling requirements proposed by the rapporteur

Physical and chemical properties

None

Classification of the preparation on the basis of toxicological properties

Classification proposal according to Directive 1999/45/EEC

Hazard symbol: X_i

Indication of danger: Irritant

Risk phrases: R38 Irritating to skin ,
R43 May cause sensitisation by skin contact)

Safety phrases: S24/25 Avoid contact with skin and eye
S37 Where suitable gloves

Justification for classification: R38 is required on the basis on the observations (mean score of 2 for erythema or oedema observed in at least two of the three animals tested) in a standard skin irritation study in rabbits. R43 is required on the basis of a positive result ($SI \geq 3$) in a local lymph node assay.

Classification proposal according to Regulation 1272/2008

Pictogram: GHS07

Signal word: Warning

Hazard class: Skin Sensitisation Category 1B

Hazard statements: H317 May cause an allergic skin reaction

Justification: Skin Sensitisation Category 1B is justified on the basis of the results ($SI \geq 3$, EC₃ >2%) of a local lymph node assay.

The personal protective equipment (PPE) requirements arising from the classification of 'GF-2573' (Xi Irritant, R38 'Irritating to skin', R43 'May cause sensitisation by skin contact' and H317 'May cause allergic skin reaction') are as follows.

- Operators must wear suitable protective clothing (coveralls), suitable protective gloves when handling the concentrate.

Classification of the preparation for environmental effects

Provisional hazard Classification/Labelling of plant protection products according to 1999/45/EEC

'GF-2573' (1999/45/EEC)		
Hazard symbol:		Dangerous for the environment
Risk phrases:	R 50/53	Very toxic to aquatic organisms, may cause long term adverse effects in the aquatic environment.
Safety phrases:	S35	This material and its container must be disposed of in a safe way.
	S57	Use appropriate containment to avoid environmental contamination.
	S59	Refer to manufacturer/supplier for information on recovery/recycling
Justification for the proposals:		
Risk phrases:	R 50	<i>Myriophyllum spicatum</i> 14 d ErC50 = 0.0844 mg formulation/L (< 1 mg/L)
	R53	Active substance not readily biodegradable
Safety phrases:	S35/57	Recommended for products that may cause effects in the environment
	S59	Recommended for all dangerous substances recommended for recovery/recycling but <u>obligatory</u> for substances classified as dangerous for the ozone layer (R59)

The product labels should carry the wording from Article 10, section 1.2 of Directive 1999/45/EC:

'To avoid risks to man and the environment, comply with instructions for use'

and the Annex V of Directive 91/414/EEC 'General provisions' phrase, SP1:

'Do not contaminate water with the product or its container (Do not clean application equipment near surface water/Avoid contamination via drains from farmyards and roads).'

Provisional Hazard Classification/Labelling of plant protection products according to Regulation (EC) 1272/2008

Pictogram	GHS09
Signal word	Warning
Hazard statements	H410: Very toxic to aquatic life with long lasting effects (acute/chronic category 1).
Precautionary statements	P391 Collect spillage

P501 Dispose of contents/ container to ... (in accordance with local/ regional/ national/ international regulation (to be specified))

Justification for product ('mixture') classification according to Regulation (EC) 1272/2008:

H 410	Required as 'GF-2573' is an 'acute category 1' and 'chronic category 1' formulation, as defined by: i) <i>Myriophyllum spicatum</i> 14 d $E_r C_{50} = 0.0844$ mg/L ii) <i>Myriophyllum spicatum</i> 14 d $NOEC_r = 0.00732$ mg/L iii) Active substance not 'rapidly biodegradable'
GHS09 Pictogram	Required for 'chronic category 1' mixture
No signal word	Required for 'chronic category 1' mixture
P 391, P 501	Required for 'chronic category 1' mixture. 'P273' not required since mixture (product) is intended for use in the environment.

2.2 Methods of analysis

Methods of analysis have been submitted in support of post-registration monitoring and control for components included in the residue definition for plants and animals. The proposed residue definition for Risk Assessment and Enforcement/Monitoring in plants and livestock is XDE-729 methyl and XDE-729 acid.

2.2.1 Analytical methods for analysis of the active substance as manufactured (Laboratory Project ID: DECO ML AL-2012-003865)

An analytical method was validated for the determination of XDE-729 in technical grade XDE-729. An internal standard high performance liquid chromatographic (HPLC) gradient method with UV detection (270 nm) was used. Quantitation was made by peak area measurements with internal standardization. The method was satisfactorily validated in terms of precision, accuracy, specificity and linearity in accordance with SANCO 3030/99 rev. 4.

Please refer to the Confidential Information (Annex C/Volume 4) for methods of analysis for impurities in the technical material.

2.2.2 Analytical methods for formulation analysis (Laboratory Study ID: DAS-AM-G-10-34).

An analytical method was validated for the determination of XDE-729 and cloquintocet-Mexyl in GF-2573 and GF-2685. An internal standard high performance liquid chromatographic (HPLC) method with UV detection (300 nm) was used. Quantitation was made by peak area measurements with internal standardization.

The method was satisfactorily validated in terms of precision, accuracy, specificity and linearity in accordance with SANCO 3030/99 rev. 4.

2.2.3 Analytical methods for residue analysis

Multi-residue Method Testing for the Determination of XDE 729 Methyl Ester and XDE 729 Acid in Plant Matrices (Dow AgroSciences LLC Study Number 110293, Eurofins Analytical Services Study Number S11-02423)

Independent Laboratory Validation of the Multi-residue Method for the Determination of XDE-729 Methyl Ester and XDE-729 Acid in Plant Matrices (Dow AgroSciences LLC Study Number 110712, PTRL Europe Study Number P 2399 G)

A QuEChERS multi-residue method was proposed in support of post-registration monitoring for the quantitative determination of residues of XDE-729 methyl ester and XDE-729 acid in agricultural commodities representative of the four European crop groupings. The validated limit of quantitation was 0.01 mg/kg.

Samples were analysed by LC/MS/MS, monitoring two MS/MS transitions characteristic of each analyte.

The QuEChERS method was validated in all areas; however, it was noted that although the mean recoveries for the acidic crop were acceptable, individual recoveries for the quantitation and confirmatory transitions for detection on XDE-729 acid in this matrix were low.

Storage stability of final sample extracts demonstrated unacceptable levels of degradation for the determination of XDE-729 methyl ester in barley grain (after 9 days) and in kale leaves (after 10 days). It is also noted that mean recovery of the XDE-729 acid in oilseed is outside acceptable recovery levels, since the initial recovery was low; therefore a small amount of degradation resulted in a recovery that is outside acceptable limits following storage after 7 days.

A corresponding ILV study was submitted as part of the validation of the method. According to SANCO/825/00 rev.8.1, an ILV must be conducted with samples of representative commodities of all matrix groups for which the primary method is required, with the same number of samples and fortification levels. If the primary method is identical for all matrix groups, it is sufficient to perform the ILV for commodities of two of these groups, one of them with high water content. In this instance, the primary method is not the same for all commodities; however, the ILV study has selected two matrix groups that allow demonstration of both procedures. Given that the representation use is cereal, and the method is not the

same for all matrix types, it is considered that ideally a dry crop should have been considered in the ILV study. In this instance however, given that the method for a wet crop (cabbage) is the same as the method for cereal, the RMS considers the ILV study is acceptable.

Enforcement Method for the Determination of XDE-729 Methyl Ester and XDE-729 Acid in Plant Matrices (Dow AgroSciences LLC Study Number 110004)

Independent Laboratory Validation of the Enforcement Method for the Determination of XDE 729 Methyl Ester and XDE 729 Acid in Plant Matrices (Dow AgroSciences LLC Study Number 110825, Pyxant Labs Study Number 2386)

This method was submitted in support of both pre-registration data requirements and post-registration monitoring, and is applicable for the quantitative determination of residues of XDE-729 methyl ester and XDE-729 acid in agricultural commodities representative of the four European crop groupings and wheat processed products. The validated limit of quantitation was 0.01 mg/kg. Samples were analyzed by liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC/MS/MS), monitoring two MS/MS transitions characteristic of each analyte and one MS/MS transition characteristic of each internal standard (the method employs a mixed stable-isotope internal standard).

It is noted that full validation data are only obtained for the primary (quantitation) MS/MS transition. According to SANCO/825/00 rev. 8.1 the additional confirmatory transition should also be validated for calibration data, recovery and precision data for samples fortified at the LOQ (n=5) and for 2 blank samples. It is a short coming of the study that full validation data has only been presented for the primary transition; however, this data has been presented for high water and high oil matrices for the ILV of this method. Only two matrices were considered in the ILV, however the primary extraction method is the same for all matrices therefore this is acceptable. Given that the ILV study report demonstrates that both the quantitative and confirmatory MS/MS transitions are acceptably validated, in this instance the RMS proposes that consideration of the complete data set from the validation report (Study Number 110004) and the ILV report (Study Number 2386) indicates that the method is fit for purpose according to SANCO/825/00 rev. 8.1. (For information, the notifier has since informed the RMS "the report will be revised to include the confirmatory transition data, including calibration, recovery and precision. The revised version will be available by June 2013". In the absence of this report at the time of submission, for the reasons shown above, the method may still be considered fit for purpose according to SANCO/825/00 rev. 8.1).

The method however does rely on stable isotope labelled internal standards. According to SANCO/825/00 rev. 8.1, all analytical standard materials used in an analytical method must be commonly available. This applies to stable isotope labelled compounds or other internal standards. If a standard is not commercially available the standard should be made generally available by the applicant and the contact details be provided. The notifier was contacted during this evaluation

however, and confirmed that the stable isotope labelled internal standards would be made available in line with guidance.

As discussed above, acceptable ILV data has been submitted.

Multi-residue Method Testing for the Determination of XDE-729 Methyl Ester and XDE-729 Acid in Animal Matrices (Dow AgroSciences LLC Study Number 110574, Eurofins Analytical Services Study Number S11-02424)

This QuEChERS multi-residue method was submitted in support of post-registration monitoring, and is applicable for the quantitative determination of residues of XDE-729 methyl ester and XDE-729 acid in animal matrices including bovine muscle, bovine kidney, bovine liver, bovine whole milk, poultry muscle, and poultry eggs. The validated limit of quantitation of 0.01 mg/kg.

Samples were analyzed by liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC/MS/MS), monitoring two MS/MS transitions characteristic of each analyte.

The QuEChERS method has been validated in all areas according to SANCO/825/00 rev. 8.1. It is noted that extraction efficiencies have not been addressed as part of the method validation; however, residues are not expected to be found in products of animal origin for the proposed use. Therefore, extraction efficiency does not need to be addressed for this evaluation. This will need to be addressed in future however if new uses give rise to positive residues.

Multi-residue Method Testing for the Determination of XDE 729 Methyl Ester and XDE 729 Acid in Bovine Fat (Dow AgroSciences LLC Study Number 110750, Eurofins Analytical Services Study Number S11-03369)

This QuEChERS multi-residue method was submitted in support of post-registration monitoring, and is applicable for the quantitative determination of residues of XDE-729 methyl ester and XDE-729 acid in bovine fat. The validated limit of quantitation was 0.01 mg/kg.

Samples were analyzed by liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC/MS/MS), monitoring two MS/MS transitions characteristic of each analyte.

The QuEChERS method has been validated in all areas according to SANCO/825/00 rev. 8.1, and the study report was well presented.

Independent Laboratory Validation of the Multi-residue Method for the Determination of XDE 729 Methyl Ester and XDE 729 Acid in Animal Matrices (Dow AgroSciences LLC Study Number 110294, PTRL Europe Study Number P 2172 G)

The objective of the ILV study was to independently validate the multi-residue method for the determination of XDE-729 methyl ester and XDE-729 acid in animal matrices. The method was Eurofins Agrosciences Services multi-residue method (Study Number S11-02424), "Validation of a Multi-Residue Method for the Determination of XDE-729 Methyl Ester and XDE-729 Acid in Animal Matrices" and Eurofins Agrosciences Services multi-residue method (Study Number S11-03369), "Validation of a Multi-Residue Method for the Determination of XDE-729 Methyl Ester and XDE-729 Acid in Bovine Fat."

The ILV study was acceptable. For information, it was noted that "*The API 5500 LC-MS/MS system showed a very high sensitivity especially for the determination of XDE-729 methyl ester. Thus, it was necessary to further dilute extracts fortified with this analyte (additional dilution factor: 5: 0.20 mL of extract was diluted with 0.80 mL of acetonitrile/0.1 % formic acid (1/9, v/v)) to be within the linear range of the LC-MS/MS calibration curves used*". This is considered to be a minor modification that does not impact on the validity of the study.

Enforcement Method for the Determination of XDE 729 Methyl Ester and XDE 729 Acid in Animal Matrices (Dow AgroSciences LLC Study Number 110505)

Independent Laboratory Validation of the Enforcement Method for the Determination of XDE 729 Methyl Ester and XDE 729 Acid in Animal Matrices (Dow AgroSciences LLC Study Number 110828, CEMAS Study Number CEMS-5325)

This method was submitted in support of both pre-registration and post-registration monitoring, and is applicable for the quantitative determination of residues of XDE-729 methyl ester and XDE-729 acid in bovine and poultry tissues. The validated limit of quantitation was 0.01 mg/kg.

Samples were analyzed by liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC/MS/MS), monitoring two MS/MS transitions characteristic of each analyte and one MS/MS transition characteristic of each internal standard (the method employs a mixed stable-isotope internal standard).

It is noted that full validation data are only obtained for the primary (quantitation) MS/MS transition. According to SANCO/825/00 rev. 8.1 the additional confirmatory transition should also be validated for calibration data, recovery and precision data for samples fortified at the LOQ (n=5) and for 2 blank samples. It is a short coming of the study that full validation data has only been presented for the primary transition; however, this data has been presented for bovine fat, bovine liver and poultry eggs for the ILV of this method (Study Number 110828). Only

three matrices were considered in the ILV, however the primary extraction method is the same for all matrices therefore this is acceptable. Given that the ILV study report demonstrates that both the quantitative and confirmatory MS/MS transitions are acceptably validated, in this instance the RMS proposes that consideration of the complete data set from the validation report Study Number 110505 and the ILV report (Study Number 110828) indicates that the method is fit for purpose according to SANCO/825/00 rev. 8.1.

The method however does rely on stable isotope labelled internal standards. According to SANCO/825/00 rev. 8.1, all analytical standard materials used in an analytical method must be commonly available. This applies to stable isotope labelled compounds or other internal standards. If a standard is not commercially available the standard should be made generally available by the applicant and the contact details be provided. The notifier was contacted during this evaluation however, and confirmed that the stable isotope labelled internal standards would be made available in line with guidance.

As discussed above, an ILV study was submitted, and all data contained therein are acceptable.

Description of methods for analysis of soil for parent compound and metabolites of toxicological, ecotoxicological or environmental concern (Dow AgroSciences LLC Study Number 110716)

Independent Laboratory Validation of the Method for the Determination of XDE-729 Methyl Ester and Metabolites in Soil (Dow AgroSciences LLC Study Number 120894)

This method was submitted in support for both pre-registration data requirements and post-registration monitoring, and is applicable for the quantitative determination of residues of XDE-729 methyl ester and its metabolites, XDE-729 acid and X11449757 in accordance with the residue definition in soil, in 4 soil types. The validated limit of quantitation was 0.05 µg/kg.

Samples were analyzed by liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC/MS/MS), monitoring two MS/MS transitions characteristic of each analyte and one MS/MS transition characteristic of each internal standard (the method employs a mixed stable-isotope internal standard).

The method has been validated in all areas according to SANCO/825/00 rev. 8.1.

The mean recovery of X11449757 at 0.05 µg/kg (LOQ) in clay loam, silt loam and clay, and at 8.0 µg/kg in clay loam were below the acceptable mean recovery level of 70 %. The lowest mean recovery at LOQ was 63 %. The mean recovery for all other samples and precision were all acceptable. Overall, given that the data in all other areas of the validation are well within guideline acceptable limits, and recovery of the other samples gave consistent values within acceptable limits, it is

considered in this instance to accept that the data-set, as a whole, is adequately validated for recovery and precision.

The method however does rely on stable isotope labelled internal standards.

According to SANCO/825/00 rev. 8.1, all analytical standard materials used in an analytical method must be commonly available. This applies to stable isotope labelled compounds or other internal standards. If a standard is not commercially available the standard should be made generally available by the applicant and the contact details be provided. The notifier was contacted during this evaluation however, and confirmed that the stable isotope labelled internal standards would be made available in line with guidance.

An acceptable ILV study was provided for the method. The primary method is identical for all matrix groups, therefore it was considered to be sufficient to perform the ILV on 2 soil types (sand and clay). The method has been validated in all areas according to SANCO/825/00 rev. 8.1.

Description of methods for analysis of water (drinking water, ground water and surface water) for parent compound and metabolites of toxicological, ecotoxicological or environmental concern (Dow AgroSciences LLC Study Number 110718).

Independent Laboratory Validation of the Method for the Determination of XDE-729 Methyl Ester and Metabolites in Water (Dow AgroSciences LLC Study Number 110827)

This method is applicable for the quantitative determination of residues of XDE-729 methyl ester and its metabolites, XDE-729 acid, X11449757, and X11406790, in line with the residue definition in water, in drinking water, ground water, and surface water. The validated limit of quantitation was 0.05 µg/L.

Samples were analyzed by liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC/MS/MS), monitoring two MS/MS transitions characteristic of each analyte and one MS/MS transition characteristic of each internal standard (the method employs a mixed stable-isotope internal standard).

The relative standard deviation of X11406790 in ground water at 0.05 µg/L (LOQ), was 22%, which is slightly above the normal acceptance criteria of 20%.

It is noted that full validation data are only obtained for the primary (quantitation) MS/MS transition. According to SANCO/825/00 rev. 8.1 the additional confirmatory transition should also be validated for calibration data, recovery and precision data for samples fortified at the LOQ (n=5) and for 2 blank samples. It is a short coming of the study that full validation data has only been presented for the primary transition; however, this data has been presented in the ILV of this method (Study Number 110827). Given that the ILV study report demonstrates that both the quantitative and confirmatory MS/MS transitions are acceptably validated, in this instance the RMS proposes that consideration of the complete data set from the

validation report Study Number 110718 and the ILV report (Study Number 110827) indicates that the method is fit for purpose according to SANCO/825/00 rev. 8.1. The method however does rely on stable isotope labelled internal standards. According to SANCO/825/00 rev. 8.1, all analytical standard materials used in an analytical method must be commonly available. This applies to stable isotope labelled compounds or other internal standards. If a standard is not commercially available the standard should be made generally available by the applicant and the contact details be provided. The notifier was contacted during this evaluation however, and confirmed that the stable isotope labelled internal standards would be made available in line with guidance.

Description of methods for analysis of air for active substance and metabolites, formed during or shortly after application, of toxicological concern (Dow AgroSciences LLC Study Number 110028, PTRL Europe Study Number P 2169 G)

This method has been submitted in support of post-registration monitoring, and is applicable for the quantitative determination of residues of XDE-729 methyl ester and XDE-729 acid in line with the residue definition of air, in ambient and humid warm air. The validated limit of quantitation was $0.82 \mu\text{g}/\text{m}^3$.

Samples were analyzed by liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC/MS/MS), monitoring two MS/MS transitions characteristic of each analyte.

The method has been validated in all areas according to SANCO/825/00 rev. 8.1.

Analytical methods for parent compound and toxicologically, ecotoxicologically or environmentally significant metabolites in body fluids and tissues

A method was submitted for body fluids and tissues; however, it has not been relied upon since XDE-Me is not classified as toxic or highly toxic; therefore monitoring methods for human tissues and body fluids are not required.

2.3 Impact on human and animal health

2.3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities contained in the active substance or to their transformation products

XDE-729 Acid and XDE-729 Methyl are rapidly and extensively absorbed following oral administration in rats, with plasma C_{max} occurring in the rat within 30 minutes post-dosing. Absolute oral bioavailability, calculated from the dose-corrected plasma AUC data for the low oral and IV dose groups is close to 100% for both female and male rats. In dogs, absorption XDE-729 Acid is fairly rapid with t_{max} at 0.5 to 1 hour post-dosing for both sexes. Oral bioavailability in the dog

is also high with about 80% of the administered dose of XDE-729 Acid eliminated in the urine.

The presence of a high proportion of administered radioactivity in the blood plasma indicates widespread systemic circulation of both XDE-729 Na salt and XDE-729 Methyl metabolites. There is no evidence of preferential distribution to any particular tissue, or of accumulation. Foetal exposure to XDE-729 Acid in systemic circulation is demonstrated.

Metabolism of XDE-729 Acid is limited in rats, mice and dogs evidenced by the parent compound being the major radiolabelled component in urine and faeces, accounting for 82-98% of administered dose in rats. Minor metabolites of XDE-729 Acid are the acyl-glucuronide conjugate of XDE-729 (accounting for up to ~7% of radioactivity dose in rats) and O-demethyl-XDE-729 and the corresponding sulphate and glucuronide conjugates (~6% of dose). The major radiolabelled component present in urine and faeces following oral administration of XDE-729 Methyl is also XDE-729 Acid (DAS metabolite code X11449757), demonstrating that XDE-729 Methyl is rapidly and extensively hydrolysed to XDE-729 Acid. The Acid accounts for about 80% of administered radioactivity, in males and females, respectively. As is the case for XDE-729 Acid, minor metabolites of XDE-729 Methyl are the acyl-glucuronide conjugate of XDE-729 (accounting for up to ~6% of radioactive dose) and O-demethyl-XDE-729 (X11449757) and the corresponding sulphate and glucuronide conjugates (up to ~11%). The primary analyte in blood samples is XDE-729 Acid, with no parent compound being detected, confirming the rapid hydrolysis of XDE-729 Methyl in vivo and providing evidence of post-hepatic systemic bioequivalence between XDE-729 Acid and XDE-729 Methyl. Toxicokinetic investigations in the 90-day oral dietary study in the rat (JIA 5.3.2/02) identified an additional metabolite of XDE-729 Methyl, the glucuronide conjugate of demethyl XDE-729 Methyl (metabolite code for demethyl XDE-729 Methyl is X11406790), detected in blood, liver and urine. The amount of this metabolite excreted in urine in females accounts for up to 5.5% of the dose of XDE-729 Methyl (adjusted for equivalence) at a dose level of 3 mg/kg/day and 12.4% at 500 mg/kg/day. This indicates that not all administered XDE-729 Methyl undergoes hydrolysis to XDE-729 Acid, even at dose levels as low as 3 mg/kg/day.

For XDE-729 Methyl administration by the dermal route, systemic exposure is shown also to be primarily to XDE-729 Acid following application of concentrations up to 7.5 g/L for 10 hours.

Absorbed XDE-729 Acid is rapidly and extensively excreted mainly via urine (68-92% of the administered dose), with the proportion in urine being highest among females. The majority of the urinary elimination occurs within the first 24 hours post-dosing. A smaller percent of the oral dose is eliminated in faeces, the majority of which (78-93%) occurred within 24 h of dosing. The extent and rates of urinary and faecal elimination of absorbed XDE-729 Methyl is similar to the XDE-729 Acid salts.

The acute toxicity, irritancy and skin sensitisation potential of XDE-729 Acid and XDE-729 Methyl have been investigated in standard GLP and OECD guideline compliant studies. These studies showed that both XDE-729 Acid and XDE-729 Methyl are of low acute oral and dermal toxicity, with LD₅₀ values above those required for classification, and that neither is irritating to the skin and eye or show skin sensitising potential. Acute inhalation studies were not conducted because it is not technically possible to generate respirable test atmospheres; furthermore, human inhalation exposure is unlikely as both XDE-729 Acid and XDE-729 Methyl are classed as very slightly volatile.

The oral dietary studies demonstrate that the main target organ for XDE-729 Acid is the kidney in rats and dogs. The primary changes in the rat kidney are renal tubular degeneration together with hypertrophy and vacuolation of the collecting duct epithelium. In the dog, degenerative and regenerative changes in the tubules and slight degeneration of collecting ducts are induced at 28 and 90 days and, additionally, slight fibrosis or focal granuloma in cortex and slight glomerulosclerosis at 1 year. Other findings in the dog include decreased red blood cell (RBC) mass and subsequent extramedullary hematopoiesis in the spleen and liver. In mice the only noteworthy finding are a slight inflammation of the urinary bladder mucosa in the 90 day study and a reduction in red blood cell count in the 26 day study. The most sensitive NOAELs are 252 mg/kg/day in rats, 11 mg/kg/day in dogs and 269 mg/kg/day in mice. By the dermal route, XDE-729 Acid does not cause local effects or systemic toxicity in rats. Inhalation studies have not been conducted because XDE-729 Acid and XDE-729 Methyl are non-volatile substances and inhalation is not expected to be a significant route of exposure to humans.

In contrast, oral dietary studies identify the liver as the main target for XDE-729 Methyl in rats. The primary changes in the liver are hepatocyte hypertrophy, mitotic figures and vacuolisation consistent with fatty change, observed at exposure levels of 52 mg/kg/day and above. Other targets, affected only at higher exposure levels, are kidneys, thyroids, thymus and blood. The kidney changes are slight multifocal hypertrophy of collecting duct epithelial cells; for the thyroid, organ weight is increased, accompanied by a diffuse hypertrophy of follicular cells; in the thymus, lymphoid tissue atrophy are induces; in blood, haemoglobin concentration, haematocrit and red cell count are reduced. For XDE-729 Methyl, a short-term oral NOAEL of 10 mg/kg/day is identified for liver toxicity is identified in the repeated dose toxicity studies, based on the presence liver toxicity in rat at 52 mg/kg/day. However, in the XDE-729 Methyl rabbit developmental toxicity study a lower oral dietary NOAEL for maternal toxicity of 5.78 mg/kg/day was identified, based on the observation of increased liver weight and slight hypertrophy and altered tinctorial properties of periportal hepatocytes at 18.5 mg/kg/day.

The genotoxicity of XDE-729 Acid has been adequately investigated in the standard tests. This substance tests negative in *in vitro* assays for gene mutation and clastogenicity and in an *in vivo* micronucleus test. It is therefore concluded that XDE-729 Acid is not genotoxic. XDE-729 Methyl also tests negative in standard *in vitro* assays for gene mutation and clastogenicity, and it can therefore be concluded

that XDE-729 Methyl is not genotoxic. A technical batch of XDE-729 Methyl (Lot 201101758-63B, TSN302167, 93.3% purity) is negative in an *in vitro* bacterial assay for gene mutation.

A standard carcinogenicity study in the rat and one in the mouse demonstrate that XDE-729 Acid is not carcinogenic. This conclusion is also applicable to XDE-729 Methyl at oral exposure levels of up to 10 mg/kg/day.

Regarding the long-term non-neoplastic toxicity, kidneys are identified as the principal target for XDE-729 Acid in the rat, as is the case for short-term exposure. Kidney changes occur at exposure levels of 400 mg/kg/day and above. The kidney effects seen at 12 months are chronic progressive glomerulonephropathy, hyperplasia of the pelvic epithelium, hypertrophy of collecting duct epithelium, increased number of mitotic figures in the collecting duct epithelium, chronic interstitial inflammation of the medulla, necrosis of collecting duct epithelium and vacuolization of collecting duct epithelium in the papilla, accompanied by increased kidney weight. Additional pathology changes in the kidney are observed at 24 months, namely tubular degeneration with regeneration and necrosis of individual tubular epithelial cells and, in occasional males, the presence of calculi in the pelvis. At 24 months there are also changes in the urinary bladder, characterised by hyperplasia of the transitional epithelium and inflammation in the submucosa beneath the hyperplastic epithelium and, in one animal, the presence of microscopic calculi in the lumen. Secondary to the kidney toxicity, slight hypertrophy and vacuolisation of the adrenal zona glomerulosa is seen at 24 months. The kidney toxicity is accompanied by reduced bodyweight gain from 400 mg/kg/day and increased urinary volume and, at the highest dose level, increased blood urea nitrogen and reduced survival. A NOAEL of 102 mg/kg/day (target 100 mg/kg/day) is identified for the long-term toxicity of XDE-729 Acid in the rat.

In mice the urinary bladder and kidneys are identified as the principal toxicity targets of XDE-729 Acid, affecting only males. At 250 mg/kg/day and above inflammation of the urinary bladder and microscopic calculi are present in the urinary bladder lumen of males. At 750 mg/kg/day the effects on the urinary bladder are additionally characterised by hyperplasia, increased numbers of mitotic figures, necrosis of individual cells and ulceration of the transitional epithelium; also, kidney tubular degeneration with regeneration and dilatation were present. The urinary bladder and kidney toxicity is associated with increased mortality among males at 750 mg/kg/day. Treatment-related hypertrophy of the intercalated cells of the kidney was present in males at 750 mg/kg/day and females at 250 and 1000 mg/kg/day; this is interpreted as being an adaptive response, possibly related to maintaining acid-base homeostasis. NOAELs of 50 mg/kg/day in males and 1004 mg/kg/day (target 1000 mg/kg/day) in females are identified for the long-term toxicity of XDE-729 Acid in the mouse.

The reproductive toxicity of XDE-279 Acid has been adequately investigated in a rat two generation study and in a rat developmental toxicity study and a rabbit developmental toxicity study. Also, the developmental toxicity of XDE-279 Methyl has been investigated in a rat and a rabbit study. The two generation study demonstrates that XDE-729 Acid does not have an adverse effect on fertility or

general reproductive performance and classification for this endpoint is not warranted. A NOAEL of 443 mg/kg/day, the highest dose level investigated, is identified for effects on fertility and general reproductive performance. This conclusion can be extrapolated to XDE-729 Methyl. In the rat, there is evidence that both XDE-729 Acid and XDE-729 Methyl can cause marginal developmental effects, such as a slight ossification delay or slightly reduced foetal weight, but only in association with maternal toxicity. In the rabbit, XDE-729 Acid does not cause developmental toxicity; however, XDE-729 Methyl causes developmental toxicity, manifested as reduced foetal weight and a slight ossification delay, at an exposure level that also causes slight maternal liver toxicity. NOAELs for developmental toxicity of 159 mg/kg/day for XDE-729 Acid (based the rat study) and 18.5 mg/kg/day for XDE-729 Methyl (based on the rabbit study) are identified. As the only developmental changes observed for both XDE-729 Acid and XDE-729 Methyl occurred in association with maternal toxicity, and were of the type that can be assumed to secondary non-specific consequences of maternal toxicity, the criteria for classification for developmental toxicity are not met.

No evidence of specific irreversible neurotoxicity has been observed in an acute and a 90 day neurotoxicity study on XDE-729 Acid or in the general toxicity studies XDE-729 Acid and XDE-729 Methyl.

Dietary administration of XDE-729 Methyl for 28 days to the rat at dose levels of up to 500 mg/kg/day did not elicit immunotoxicity, based on the absence of an influence the primary immune response to sheep red blood cells.

The core registration toxicological studies were conducted with XDE-729 Acid. Bridging studies have been conducted with XDE-729 Methyl with the aim of demonstrating toxicological equivalence between XDE-729 Acid and XDE-729 Methyl. The bridging studies included a toxicokinetics study in rats, genotoxicity studies, acute toxicity studies, a 28-day and 90 day repeat exposure (oral dietary) studies, and a developmental toxicity study in both the rat and rabbit.

Toxicokinetic investigations in rats, mice and rabbits demonstrated that post-hepatic systemic exposure following oral administration of XDE-729 Methyl is mainly to XDE-729 Acid, and that the systemic levels are quantitatively similar following oral administration of equivalent doses of XDE-729 Methyl and XDE-729 Acid (i.e. XDE-729 Methyl and XDE-729 Acid have 'toxicokinetic equivalence'). XDE-729 Methyl and XDE-729 Acid have also been shown to be toxicologically equivalent for acute toxicity and genotoxicity endpoints, and both do not cause specific developmental toxicity in rats and rabbits. However, on 28 and 90 day repeated oral dietary administration in rats XDE-729 Methyl and XDE-729 Acid have different main toxicity target organs; for XDE-729 Methyl it is the liver (short-term NOAEL 10 mg/kg/day) and for XDE-729 Acid it is the kidney (short-term NOAEL 250 mg/kg/day in rat).

Mode of action (MoA) studies with XDE-729 Methyl demonstrated that the liver effects are mediated through activation of the aryl hydrocarbon receptor (AhR). The Applicant conducted additional MoA studies to investigate the AhR-mediated

MoA and hydrolysis of XDE-729 Methyl to XDE-729 Acid both *in vivo* and *in vitro* studies across multiple species.

Integrating the results of the MoA studies, the bridging studies and core registration studies, it can be concluded that:

1. Systemic (post-hepatic) exposure following dietary intake of XDE-729 Methyl is to XDE-729 Acid

Additional toxicokinetic investigations consistently confirm the presence of negligible levels of XDE-729 Methyl in blood or urine of rats, mice and rabbits in a wide range of studies at various oral dose levels of XDE-729 Methyl, ranging from 10 to 782 mg/kg/day. These data demonstrate that post-hepatic systemic exposure following the administration of XDE-729 Methyl is mainly to its hydrolysis product XDE-729 Acid. Evidence of systemic exposure to a direct metabolite of the parent, namely a glucuronide conjugate of O-demethyl XDE-729 Methyl, has been seen in some XDE-729 Methyl rat studies, but this conjugate was present in blood only at dose levels above the rat NOAEL of 10 mg/kg/day and no free O-demethyl XDE-729 Methyl has been detected in blood, liver or urine at any exposure level of XDE-729 Methyl, indicating low toxicological concern for this direct metabolite, certainly at the rat NOAEL for liver toxicity of 10 mg/kg/day. Overall, in relation to potential effects in the organs other than the gastrointestinal tract (local effects) and liver, the toxicity studies on XDE-729 Acid in rats, mice and rabbits can be regarded as predictive for XDE-729 Methyl for the oral route, especially at dose levels of 10 mg/kg/day and below.

PBPK modelling predicted comparable peak concentrations and 24-hr AUCs of XDE-729 Methyl in liver and blood between rats and humans at XDE-729 Methyl dietary exposure levels of 0.0001, 0.1 and 10 mg/kg/day, providing evidence that in humans systemic exposure is also mainly to the hydrolysis product. The PBPK modelling also predicted negligible (i.e. considerably below the LOQ) liver and post-hepatic systemic exposure to XDE-729 Methyl at a human exposure levels of 0.0001 and 0.1 mg/kg/day, exposure levels relevant to predicted human exposure and a proposed ADI, respectively.

2. Hepatic exposure to XDE-729 Methyl causes AhR-mediated liver toxicity and the 90-day dietary rat study defined the NOAEL for these effects as 10 mg/kg/day in the rat

In a XDE-729 Methyl 90 day dietary study conducted at dose levels 3, 10, 52, 261 and 500 mg/kg/day, a NOAEL of 10 mg/kg/day was identified. At dose levels of 52 mg/kg/day and above, the induction of hepatic *Cyp1a1* gene expression was notable and liver toxicity (increased organ weight, hepatocyte vacuolation) was observed. The severity of the hepatic changes correlated with the levels of XDE-729 Methyl detected in the liver. Thyroid changes were observed in the 90-day rat study, from 261 mg/kg/day, interpreted as being secondary to increased glucuronidation in the liver because markedly increased hepatic *Ugt1a6* gene expression was seen from 261 mg/kg/day. The induction of hepatic *Cyp1a1* and *Ugt1a6* gene expression, which correlated with the observed liver and thyroid

changes, provides evidence of activation of the AhR signalling pathway. A 28-day dietary MoA study in rats showed that XDE-729 Methyl induced liver toxicity, hepatocellular proliferation, and hepatic *Cyp1a1* gene expression which are reversible after a short recovery period.

Comparison of the results of 7 day dietary toxicity in rats and mice indicate that mice are less sensitive than rats to XDE-729 Methyl induced liver toxicity and hepatic *Cyp1a1* gene expression in relation to a short exposure period.

3. *XDE-729 Methyl is the AhR agonist and not an impurity, metabolite or XDE-729 acid*

AhR transactivation assays demonstrate that XDE-729 Methyl is a weak AhR agonist in a mouse reporter cell line and essentially has no activity in a human reporter cell line. The agonist activity of the XDE-729 Methyl samples is not quantitatively influenced by the level of purity, indicating that it is unlikely to be an impurity that is responsible for the observed AhR agonist activity. XDE-729 Acid has no AhR agonist activity in either the mouse or human reporter cell lines. A cell-free *in vitro* photoaffinity ligand competition-binding assay, using AhR sourced from Sprague Dawley male rat liver cytosol, demonstrates that XDE-729 Methyl is an AhR ligand in this species.

4. *Rats are significantly more sensitive to AhR activation by XDE-729 Methyl than humans*

In vitro Cyp1a1 and Cyp1a2 gene expression studies in primary cultures of freshly isolated human, mouse and rat hepatocytes provide evidence of rats being more sensitive to AhR activation by XDE-729 Methyl than humans. For expression of Cyp1a1/CYP1A1 by XDE-729 Methyl, the rat was the most sensitive and human being the least. For Cyp1a2/CYP1A2 expression, the rat was also the most sensitive, and the mouse being the least. For both enzymes, all tested species were much more sensitive to induction by the positive control, 3-MC, than by XDE-729 Methyl.

As mentioned in point 3 above, AhR transactivation assays demonstrate that XDE-729 essentially has no AhR agonist activity in a human reporter cell line. This provides additional evidence that humans may have relatively low sensitivity to AhR activation by XDE-729 Methyl.

5. *The NOAEL of 10 mg/kg/day established for AhR-mediated liver toxicity in the rat 90-day dietary study with XDE-729 Methyl is applicable to the human health risk assessment for longer-term exposures*

The 90 day XDE-729 Methyl dietary study identified a NOAEL of 10 mg/kg/day for AhR-mediated liver toxicity in the rat. A framework analysis shows that it is appropriate to make a conservative assumption that this MoA is relevant to humans. The 90 day NOAEL is considered to also be applicable for XDE-729 Methyl exposures of longer duration because there was no increase in severity of liver toxicity in the 90 day XDE-729 Methyl dietary study in rats as compared to

the 28 day XDE-729 Methyl dietary study (both studies identified NOAELs and LOAELs of 10 and ~50 mg/kg/day, respectively). This NOAEL of 10 mg/kg/day for AhR-mediated liver toxicity in rats is probably conservative in relation to humans because humans are likely to be less sensitive than rats to AhR activation and to subsequent induction of CYP1A1/CYP1A2 by XDE-729 Methyl.

Human post-hepatic systemic exposure following XDE-729 Methyl intake by the oral route will primarily be to the Acid, for which there is a full set of regulatory toxicity studies. Bridging studies are available for XDE-729 Methyl which show that XDE-729 Methyl and XDE-729 Acid are toxicologically equivalent in rats at dose levels of up to 10 mg/kg/day based on the absence of AhR-mediated effects in the liver at this dose level and below in the XDE-729 Methyl studies, although XDE-729 Methyl and XDE-729 Acid have different target organs and NOAELs at higher dose levels. Although a NOAEL of 10 mg/kg/day has been identified for AhR-mediated liver toxicity in the rat, a lower NOAEL of 5.78 mg/kg/day was identified for XDE-729 Methyl mediated liver toxicity in the rabbit in a developmental toxicity study (Ellis-Hutchings et al 2012, IIA 5.6.11/04). This lower NOAEL will be used as the starting point for deriving a dietary reference dose for the human risk assessment.

Regarding the dog, the toxicokinetics of XDE-729 Methyl have not been investigated in this species. Therefore, it must be assumed that the toxicokinetics of XDE-729 Methyl in the dog will be similar to the rat (i.e. post hepatic systemic exposure in the dog following XDE-729 Methyl is mainly to its hydrolysis product XDE-729 Acid) for the XDE-729 Acid dog studies to be regarded as predictive of the post-hepatic systemic toxicity of XDE-729 Methyl; in the opinion of the RMS, this is a reasonable assumption especially for dose levels up to the rat NOAEL of 10 mg/kg/day. To consider the liver as the target organ of XDE-729 Methyl, it is likely that the dog will be less sensitive than the rat to XDE-729 Methyl AhR-mediated liver toxicity, based on published studies showing that dog AhR has relatively low binding affinity for an AhR ligand and the absence of liver toxicity in dogs following administration of a compound which is metabolised to a potent AhR agonist.

For the dermal route of exposure to XDE-729 Methyl, systemic exposure is shown also to be primarily to XDE-729 Acid following the single application of concentrations up to 7.5 g/L for 10 hours. Therefore, the results of the oral XDE-729 Acid studies can be extrapolated to the dermal route.

No information is available on the toxicokinetics for the inhalation route. However, human exposure is likely to be to material with particle size greater than 10 µm and so inhaled particles will be cleared to the stomach rather than penetrating the deep lung. Thus, oral XDE-729 Acid studies are relevant for the inhalation route of exposure.

2.3.2 Proposal for an acceptable daily intake (ADI)

The key repeated dose adverse health effect of XDE-729 Methyl is liver toxicity, observed in rats and rabbits. In rat, the liver toxicity has been shown to be AhR mediated, with a NOAEL of 10 mg/kg/day, identified in a 90 day dietary study in rats (Stebbins et al 2012, IIA 5.3.2/02). The level of toxicity seen after 90 days exposure is similar to that found at 28 days, indicating no progression with time and therefore this NOAEL is considered applicable to chronic exposures. However, in the rabbit a lower NOAEL of 5.78 mg/kg/day was identified in a developmental toxicity study (Ellis-Hutchings et al 2012, IIA 5.6.11/04). Humans are expected to be less sensitive to the AhR-mediated liver effects seen in the rat, but the mode of action for the liver effects in the rabbit is not clear, so the standard assessment factor of 100 is deemed appropriate. Therefore, dividing the NOAEL of 5.78 mg/kg/day by 100, an **ADI of 0.058 mg/kg/day** is derived.

2.3.3 Proposal for an acute reference dose (ARfD)

The most appropriate starting point for deriving the ARfD is the NOAEL of 250 mg/kg identified in the acute oral neurotoxicity study on XDE-729 Acid (Marty et al 2010, IIA 5.7.1/01), based on the observation of slight reduced bodyweights and equivocal evidence of reduced activity several hours after dosing.

The other studies which potentially provide information on toxicity associated with acute exposure do not provide a suitable starting point for the ARfD derivation. In the general acute toxicity studies, the only dose levels investigated were much greater than the 250 mg/kg acute neurotoxicity LOAEL. Also, no adverse effects that could clearly be associated with the first few days exposure were observed in the short-term repeated dose toxicity and developmental toxicity studies.

The standard assessment factor of 100 is deemed appropriate. So, dividing the NOAEL of 250 mg/kg/day by 100, an **ARfD of 2.5 mg/kg/day** is derived.

2.3.4 Proposal for an acceptable operator exposure level (AOEL)

a) Short-term AOEL(s)

A systemic AOEL based on the NOAEL of 5.78 mg/kg/day identified in the developmental toxicity study (Ellis-Hutchings et al 2012, IIA 5.6.11/04) is proposed as this dose level is relevant to a short-term repeated exposure pattern experienced by operators. There is no reason to apply a safety factor other than the standard one of 100. Therefore, dividing the NOAEL of 5.78 mg/kg/day by 100, an **AOEL of 0.058 mg/kg/day** is derived.

b) Long-term AOEL

A long-term AOEL is not proposed, as long-term operator exposure is not anticipated. However, if a long-term AOEL is required, the value proposed for the short-term AOEL is also applicable.

2.3.5 **Proposal for a maximum allowable concentration (MAC) in drinking water / drinking water limit (DWL)**

A health-based MAC of 0.174 mg/L can be calculated, on the basis that exposure via drinking water should not exceed 10% of the ADI and assuming water consumption of 2 L/day and a bodyweight of 60 kg. However, the levels of all active substances in drinking water are limited to 0.1 µg/L under EU legislation.

2.3.6 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

2.3.6.1 Operators, bystanders and workers

Operator exposure assessments undertaken using the German model and UK POEM indicate that the proposed application of 'GF 2573' will result in an acceptable risk to operators (as detailed below)

Operator exposure to XDE-279 methyl resulting from the proposed use of 'GF-2573': summary of estimates indicating an acceptable risk

Proposed use	Application method	Model/data	Operator protection	% of AOEL
Cereals	Tractor-mounted field crop boom sprayer	German model	NO PPE	1%
		UK POEM	NO PPE	15%

On the basis of the above estimates and considering the hazard classification of the formulation, the risk to operators resulting from the proposed use of 'GF-2573' is considered to be acceptable subject to the following operator protection requirements.

- Operators must wear suitable protective gloves and coveralls when handling the concentrate.

Bystander and worker exposure assessments also indicate an acceptable level of risk, as surmised below in tables B.6.14.4-2 and B.6.14.4-3.

Bystander exposure to XDE-279 methyl resulting from the proposed use of 'GF 2573': summary of estimates indicating an acceptable risk for unprotected bystanders

Proposed use	Application method	Model/data	% of AOEL
Cereals	Tractor-mounted field crop boom sprayer	Vapour, Californian EPA surrogate study	7% adults 14% children
Cereals	Tractor-mounted field crop boom sprayer	Simulated bystander exposure measurements (Lloyd and Bell)	<1 %
Cereals	Tractor-mounted field crop boom sprayer	US EPA values for residential exposure	<1 %

Worker exposure to XDE-279 methyl resulting from the proposed use of ‘GF-2573’: summary of estimates indicating an acceptable risk for unprotected workers undertaking crop inspection activities

Proposed use	Application method	Model/data	% of AOEL
Cereals	Tractor-mounted field crop boom sprayer	EUROPOEM II worker re-entry model	2%

2.3.6.2 Consumers

See Section 2.4, below for a summary of residues in plant and animal commodities and consumer exposure conclusions.

2.4 Residues

2.4.1 Definition of the residues relevant to MRL's

Plants

Upon consideration of the plant metabolism data, mammalian toxicology data and the presented residue trials on cereals, the residue definition for MRL setting and enforcement is XDE-729 methyl and XDE-729 acid.

Based on the metabolism data submitted for wheat and turnip, residues should be defined as follows:

Crops (MRL and monitoring): XDE-729 methyl and XDE-729 acid

Animals

Upon consideration of the animal metabolism data and mammalian toxicology the following residue definition for MRL setting and enforcement is XDE-729 methyl and XDE-729 acid.

Based on the metabolism data submitted for goats and hens, residues should be defined as follows:

Animal products (MRL and monitoring): XDE-729 methyl and XDE-729 acid

2.4.2 Residues relevant to consumer safety

2.4.2.1 Plant metabolism

Primary crops

A single application of XDE-729 methyl with and without the safener cloquintocet-mexyl at an application rate of 10 g a.s./ha resulted in immature forage, hay and mature straw and grain that contained 0.09-0.20, 0.24-0.41, 0.07-0.35, and ≤ 0.004 mg/kg XR-729 methyl equivalents of the TRR, respectively.

The majority of the residues were found to be readily extractable with a mild procedure, and minimal additional residues were extractable with stronger procedures. Typically 62-77% of the residue was extracted from forage, hay and straw samples and was further characterized by HPLC. No characterization of radioactivity was performed for the grain samples due to low TRR levels (≤ 0.004 mg/kg XR-729 methyl equivalents).

The neutral ASE extract of immature forage consisted of multiple components, including parent XR-729 methyl (4-9% of the TRR), X11449757 (approx. 5% of the TRR), X11393729 (0.6-2.0 % of the TRR), X11861662 (4-5% of TRR), X11406790 (3-4% of TRR), X11406790 glucose conjugate (2-3% of the TRR), and X11406790 glucose-malonyl conjugate (X12245409, 6-10% of the TRR). The neutral ASE extract of hay and straw showed a similar HPLC profile to the forage extract. No other single component accounted for more than 4% of the TRR.

Overall, the average of the TRR identified in forage, hay and straw was 30%, 20% and 16% respectively. Whilst the level of TRR characterized (was on average 26%, 28% and 31%, given that levels in hay and straw are between 0.072-0.113 mg/kg XDE-729 methyl equivalents, the notifier was requested to address whether any single component may exceed the trigger <0.05 mg/kg for animal feed. The notifier responded stating that "No other single component accounted for more than 4% of the TRR or 0.01 mg eq/kg".

The amount of non-extractable, or bound radioactivity, was 24-29% (0.03-0.05 mg/kg XR-729 methyl equivalents), 27-30% (0.07-0.12 mg/kg XR-729 methyl equivalents), and 25-31% of the TRR (0.05-0.11 mg/kg XR-729 methyl equivalents) in forage, hay and straw, respectively.

The bound residues of forage, hay and straw were evaluated, and the results demonstrated broadly similar levels of incorporation or encapsulation of radioactivity into pectin, ADF soluble and ADF of forage, hay and straw tissue. There is slightly more radioactivity associated with lignin in the straw, which is to be expected as the plant grows. The residues in the various fractions were below the 0.05 mg/kg trigger value for animal feed; therefore were not characterised further.

There was no significant effect of the safener CQC on the transformation of XR-729 methyl in wheat.

Metabolism of XDE-729 methyl in wheat proceeds through dissociation to produce the XDE-729 acid or de-methylation of the methoxy group on the phenyl ring to produce the metabolite X11406790. X11406790 is then conjugated with glucose followed by further conjugation with malonic acid. Metabolism continues through natural incorporation of the radiolabeled carbon into natural plant constituents, such as pectin and lignin.

A metabolism study was also conducted in turnip. XDE-729 Methyl at the maximum proposed seasonal application rate resulted in mature PH-labeled roots and tops that contained 0.001 and 0.091 µg/g XDE-729 Methyl equivalents, respectively. The PY-labeled mature roots and tops contained 0.002 and 0.109 µg/g XDE-729 Methyl equivalents, respectively.

Due to the low levels of radioactivity, the roots were not analyzed further. Immature and mature foliage contained consistent metabolites at similarly low levels. In the mature foliage, the radioactive residue was identified as XDE-729 Methyl (parent) (7% of the TRR, 0.006-0.008 µg/g), X11393729 (Acid) (3% of the TRR, 0.003-0.004 µg equiv./g), glucose conjugate of X11393729 (13-14% of the TRR, 0.012-0.015 µg equiv./g), a malonyl glucose conjugate of X11406790 (7% of the TRR, 0.006-0.008 µg equiv./g), two N-glucose conjugates of XDE-729 Methyl (anomer 1: 15-17% of the TRR, 0.014-0.019 µg equiv./g, anomer 2: 9-10% of the TRR, 0.009-0.010 µg equiv./g), and X11406790 (2-3% of the TRR, 0.002 µg equiv./g). The radiolabeled metabolites were the same irrespective of radiolabel, indicating no evidence of bridge cleavage.

In summary, individual metabolite levels were low, with the majority of the radioactive residue identified as parent XDE-729 methyl, primarily conjugated through the nitrogen. Additionally, de-methylation metabolites X11393729 and X11406790, and glucose or malonyl-glucose conjugates of these metabolites were also observed. The higher amounts of conjugates relative to primary metabolites indicates that conjugation is a preferential route of metabolism. The overall metabolic pathway is consistent with the metabolic pathway observed in wheat.

Metabolism, distribution and expression of the residue in rotational crops

XDE-729 methyl radiolabeled in either the phenyl or pyridine ring was applied to plots of bare sandy loam soil at the rate of 10 g a.e./ha. At three plant-back intervals (14, 90, and 270 days) radishes, lettuce, and wheat were sown. The crops were grown outdoors to maturity at Ricerca, Ohio, USA. Plot maintenance simulated typical cultural practices.

From each plant-back interval, immature lettuce, mature lettuce, mature radish tops, mature radish roots, wheat forage, wheat hay, and wheat grain and straw were harvested. The harvested crops were milled and combusted to determine Total Radioactive Residue levels. All crop fractions harvested contained less than 0.01 mg/kg XDE-729 methyl equivalents, and were therefore not analyzed further.

It is unlikely that crops rotated into wheat fields treated with XDE-729 at 10 g a.e./ha would result in detectable levels of XDE-729 methyl or metabolites in any Raw Agricultural Commodity. Because of the low residue levels in all crops at all

plant-back intervals, a metabolic pathway has not been proposed, and a succeeding residue trials crop study and tolerance/MRL are not necessary for succeeding crops.

2.4.2.2 Animal metabolism

Ruminant (Goats)

When dosed at approximately 476 times the maximum theoretical dietary burden to dairy cattle XDE-729 methyl was rapidly eliminated in the faeces and in the urine (approximately 60-70% of the dose). Additionally, 13.0% and 7.0% of the dose was recovered in the gastrointestinal tract and contents of the PH- and PY-labelled groups, respectively. The majority of this recovered radioactivity was found in the contents of the GI tract, indicating that the radioactivity had not been absorbed. Had the GI contents been allowed to be completely digested, more radioactivity would presumably have been absorbed. Less than 0.1% of the dose was recovered in the combined milk samples, and only one milk sample (PY-labelled day 3 pm) contained greater than 0.01 mg/kg XDE-729 methyl equivalents. Analyses of milk showed the residue levels reached a plateau after 3 days. Muscle and most fats (with the exception of renal fat) contained less than 0.01 mg/kg XDE-729 methyl equivalents. Kidney and liver contained higher amounts (max 0.121 mg/kg and max 0.077 mg/kg for kidney and liver respectively).

Residues in milk and tissues were readily extractable. The sulfate conjugate of X11449757 (or isomer), X11449757, X11393729, the N- or O-glucuronic acid conjugate of X11406790 (or isomer), the N-glucuronic acid conjugate of XDE-729 methyl (or isomer), the sulfate conjugate of X11406790 (or isomer), and X11406790 were all detected in edible tissues and/or milk. Less than 0.001 mg/kg XDE-729 methyl was detected in milk or any edible tissue. Generally, greater than 61% (with the exception of ¹⁴C-PY Liver, which was 47.6%) of the residues in milk and tissues were identified as one of the above components, with the remaining residue characterized as multi-component.

Metabolism in goats proceeds through demethylation to either the carboxylic acid (X11393729) or phenol (X11406790), or both (X11449757). Parent XDE-729 methyl or metabolites may then conjugate with sulfate or glucuronic acid. The metabolic pathway of XDE-729 methyl is similar in goats, hens and rats. In the edible matrices, metabolite X11449757 was observed at the highest level, 0.048 mg/kg XDE-729 methyl equivalents, in the PH-labelled liver. Significant levels of parent and metabolites (free plus conjugated) would not be expected at levels greater than the analytical method proposed LOQ, typically 0.01 mg/kg on the basis of the proposed GAP uses.

Metabolism in goats proceeds through demethylation to either the carboxylic acid (X11393729) or phenol (X11406790), or both (X11449757). Parent XDE-729 methyl or metabolites may then conjugate with sulfate or glucuronic acid.

The proposed residue definition is XDE-729 methyl and XDE-729 acid.

Poultry

When dosed at approximately 625 times the maximum theoretical dietary burden to hens (0.016 mg/kg DM basis) XDE-729 methyl was rapidly eliminated in the excreta (94.5 and 93.8% of the dose, from the PH- and PY-labelled groups, respectively). Less than 0.1% of the dose was recovered in the combined edible matrices. Muscle and most fats contained less than 0.01 mg/kg XDE-729 methyl equivalents.

Residues in liver were readily extractable. The sulfate conjugate of X11449757 (or isomer), X11449757, X11393729, the sulfate conjugate of X11406790 (or isomer), and X11406790 were all detected. No XDE-729 methyl was detected. Less than 0.02 mg/kg XDE-729 methyl equivalents was either unextractable or characterized as being multi-component. In the edible matrices that were analyzed, metabolite X11449757 was typically observed at the highest level. Significant residues would not be expected at levels greater than the analytical method LOQ, typically 0.01 mg/kg on the basis of the proposed GAP uses.

Metabolism proceeds through demethylation to either the carboxylic acid (X11393729) or phenol (X11406790), or both (X11449757). Parent XDE-729 methyl or metabolites may then conjugate with sulfate. The metabolic pathway of XDE-729 methyl is similar in goats, hens, and rats.

The proposed residue definition is XDE-729 methyl and XDE-729 acid.

2.4.2.3 Residue definition for risk assessment**Plants**

Based on the metabolism data submitted for wheat and turnip, residues should be defined as follows:

Residue definition for consumer risk assessment:	XDE-729 methyl and XDE-729 acid.
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Other metabolites (both conjugates and non-conjugates), particularly those formed through the demethylation pathway were also considered. The notifier provided a justification to address the relevance of these low level metabolites with respect to human health on the basis of their potential for exposure and relative toxicity to parent compound.

In addition, the notifier addressed the relative toxicity of the non-conjugated metabolites X11406790 and X11449757 in comparison with XDE-729 methyl and XDE-729 acid by utilizing the concept of 'threshold of toxicological concern' (TTC) as used in the European regulation of pesticide metabolites (European Commission, 2003) and described in the open literature (Felter et al., 2009) and in an EFSA Scientific Opinion (EFSA, 2012).

A dietary exposure assessment for the metabolites X11406790 and X11449757 was also presented as further evidence that the metabolites should not be added to the residue definition for XDE-729 methyl.

Full details are given in Section B.7.17.9; however, in summary, the metabolites X11406790 and X11449757 and their conjugates are not considered to be of toxicological concern or a risk in terms of potential dietary exposure, and should not be included in the residue definition for XDE-729 methyl.

The RMS concluded that overall no toxicity concerns have been identified for the metabolites.

The opinion of the RMS is that the proposed residue definition XDE-729 methyl and XDE-729 acid is acceptable.

Animals

Based on the metabolism data submitted for goats and hens, residues should be defined as follows:

Animal products (Risk Assessment): XDE-729 methyl and XDE-729 acid

2.4.2.4 Supervised residue trials

Residue trials were conducted in winter wheat, winter barley, spring wheat and spring barley in northern and southern Europe over a two year period. In total there were 83 residue trials conducted with 22 trials in winter wheat (11 in N-EU and 11 in S-EU), 19 trials in spring wheat (10 in N-EU and 9 in S-EU), 21 trials in winter barley (10 in N-EU and 11 in S-EU) and 21 trials in spring barley (11 in N-EU and 10 in S-EU).

The representative formulation applied in these residue trials was GF-2573, an EC formulation containing XDE-729 methyl at a nominal concentration of 7.5 g acid equivalent (a.s) /L. The formulation also contains a herbicide safener, cloquintocet-mexyl, at a nominal concentration of 7.5 g a.s/L.

In the 15 winter wheat and winter barley decline trials where whole plant samples were collected for residue analysis, residues of XDE-729 methyl and XDE-729 acid in whole plants were below the limit of detection (<0.003 mg/kg) immediately before the second application in the spring, indicating that the preceding autumn application would not be expected to contribute to any residues observed in grain or straw. This conclusion is further confirmed by the finding that residue levels in grain and straw within a given winter wheat or winter barley trial are quite similar when comparing the treatment with an autumn application at 7.5 g ae/ha followed by a spring application at 6.0 g ae/ha at growth stage BBCH 45 to the treatment in which there is only a single spring application at 6.0 g ae/ha at BBCH 45.

Residues of XDE-729 methyl and XDE-729 acid typically decreased rapidly in whole plants following application in the spring, often being non-detectable (<0.003 mg/kg) by approximately 14 to 28 days after application, although in a few

trials residues in whole plants remained detectable through a final sample collection at approximately 56 days after application.

Out of 83 trials, residues of XDE-729 methyl or XDE-729 acid in grain were not detected (<0.003 mg/kg) or were <0.01 mg/kg in 82 trials (one trial (Bulgarian trial, CEMS-4720G) was accepted to be an outlier).

Residues of XDE-729 methyl and XDE-729 acid in straw were most frequently not detected (<0.003 mg/kg) or were detected, but below the LOQ (<0.01 mg/kg).

However, for the treatment compliant with the critical GAP there were 5 residue trials out of the total of 83 trials in which residues of XDE-729 methyl or XDE-729 acid were above the LOQ (>0.01 mg/kg).

Residues of cloquintocet-mexyl and cloquintocet acid were not detected (<0.005 mg/kg) in the grain or straw from any of the residue trials.

XDE-729 Methyl and XDE-729 acid: Northern Zone

Crop (situation)	Number of relevant trials	Range of residues* (mg/kg)	STMR (mg/kg)	HR (mg/kg)	Estimated MRL (Grain) (rounded value from OECD calculator)	Estimated MRL† (Straw) (rounded value from OECD calculator)
Winter Wheat	11	Grain: all samples <0.02 Straw: all samples <0.02	0.02 (Grain and Straw)	0.02 (Grain and Straw)	0.02	0.02
Winter Barley	10	Grain: all samples <0.02 Straw: all samples <0.02	0.02 (Grain and Straw)	0.02 (Grain and Straw)	0.02	0.02
Spring Wheat	10	Grain: all samples <0.02 Straw: 9 samples <0.02, one sample 0.026	0.02 (Grain and straw)	0.02 (Grain) 0.026 (straw)	0.02	0.03
Spring Barley	11	Grain: all samples <0.02 Straw: all samples <0.02	0.02 (Grain and Straw)	0.02 (Grain and Straw)	0.02	0.02

*The residue definition for both risk assessment and enforcement is XDE-729 methyl ester and XDE-729 acid. The residue level is the sum of the two components in the residue definition

†An estimated MRL for straw is shown in the table above; however, at the time of evaluation this information is not required as part of the authorization. It is for information only, with a view to when MRLs will be set for animal feed commodities in future.

XDE-729 Methyl and XDE-729 acid Southern Zone

Crop (situation)	Number of relevant trials	Range of residues* (mg/kg)	STMR (mg/kg)	HR (mg/kg)	Estimated MRL (Grain) (rounded value from OECD calculator)	Estimated MRL† (Straw) (rounded value from OECD calculator)
Winter Wheat	11	Grain: all samples <0.02 Straw: all samples <0.02	0.02 (Grain and Straw)	0.02 (Grain) 0.02 (Straw)	0.02	0.02
Winter Barley	11	Grain: all samples <0.02 Straw: 10 samples <0.02, one sample at 0.05	0.02 (Grain and Straw)	0.02 (Grain) 0.05 (Straw)	0.02	0.06
Spring Wheat	9	Grain: all samples <0.02 Straw: 8 samples <0.02, one sample 0.03	0.02 (Grain and Straw)	0.02 (Grain) 0.03 (Straw)	0.02	0.04
Spring Barley	10	Grain: all samples <0.02 Straw: 8 samples <0.02, one sample 0.025	0.02 (Grain and Straw)	0.02 (Grain) 0.025 (Straw)	0.02	0.03

*The residue definition for both risk assessment and enforcement is XDE-729 methyl ester and XDE-729 acid. The residue level is the sum of the two components in the residue definition

†An estimated MRL for straw is shown in the table above; however, at the time of evaluation this information is not required as part of the authorization. It is for information only, with a view to when MRLs will be set for animal feed commodities in future.

Frozen Storage Stability**Plant Matrices**

The frozen storage stability of XDE 729 methyl ester and its major metabolite XDE 729 acid have been determined in crops representing the four European Union crop groupings as part of an ongoing 24 month study. The crops included lettuce (a high-water crop), wheat grain (a dry crop), oilseed rape seed (an oily crop), and oranges (a high-acid crop). Data has been collected to approximately 16 months and indicates that residues of XDE 729 methyl ester and XDE 729 acid are stable, with no observable degradation.

The frozen storage stability of the safener cloquintocet-mexyl and its major metabolite cloquintocet acid have been determined in crops representing the four

European Union crop groupings as part of an ongoing 24 month study. The crops included lettuce (a high-water crop), wheat grain (a dry crop), oilseed rape seed (an oily crop), and oranges (a high-acid crop). Data has been collected to 338 days (approximately 11 months) and indicates that residues of cloquintocet-mexyl and cloquintocet acid are stable, with no observable degradation.

Animal Tissues

The frozen storage stability of XDE 729 methyl ester and its major metabolites, XDE 729 acid and X11449757, have been determined in ruminant and poultry tissues as part of an ongoing 24 month study.

For XDE 729 methyl ester and XDE 729 acid, data has been collected to approximately 12 months for bovine muscle, bovine milk, poultry liver, and poultry eggs, and indicates that XDE 729 methyl ester and XDE 729 acid are stable, with no observable degradation.

For X11449757, data has been collected to approximately 6 months for bovine muscle, bovine milk, poultry liver, and poultry eggs, and indicates that X11449757 is stable, with no observable degradation.

Soil

The frozen storage stability of XDE 729 methyl ester and its major metabolites, XDE 729 acid and X11449757, have been determined in soil (LUFA 2.2, loamy sand) as part of an ongoing 24 month study. Data has been collected to 12 months and indicates that XDE 729 methyl ester, XDE 729 acid, and X11449757 are stable, with no observable degradation.

2.4.2.5 Processing studies

Under conditions representative of processing operations, ^{14}C -XDE-729 methyl is degraded with increased pH and temperature, with formation of one degradate, X11393729, accounting for up to 29.6% of the total radioactivity. ^{14}C -X11393729 can be regarded as stable to hydrolysis. Therefore, hydrolysis during RAC processing operations does not significantly affect the nature of the residues since both XDE-729 methyl and X11393729 (XDE-729 acid) are proposed as the residue definition for XDE-729 methyl in plants.

Although the levels of residue of XDE-729 methyl and XDE-729 acid in grain from supervised residue trials do not trigger a requirement for processing studies (supervised residue trials resulted in an LOQ residue situation in grain), studies with both wheat and barley were carried out to evaluate residues in processed products. The notifier states that the processing studies were planned and carried out concurrently with the year 2 supervised residue trials as a precautionary measure in the event that any higher residue levels than expected were observed among the year 2 trial results.

There were three trials each for wheat and barley carried out to evaluate the potential for transfer of any residues from grain to processed products. For both wheat and barley, GF-2573 was applied at growth stage BBCH 45 in a single application at an exaggerated rate of XDE-729 methyl at a nominal rate 30 g ae/ha, which is 5X the maximum rate of 6 g ae/ha for application of XDE-729 methyl in

the spring. The trials for both wheat and barley were carried out in Germany, Italy and Spain. Each of the three trials for both wheat and barley were carried out as balance trials with processing following industrial procedures on a laboratory scale. The processed products of wheat that were analyzed for residues were: cleaned grain, middlings, wheat germ, fine bran, coarse bran, total bran, refined flour, white bread, wholemeal bread and wholemeal flour. The processed products of barley that were analyzed for residues were: cleaned grain, pot barley, barley bran, barley flour, brewing malt, malt sprouts, spent grain, flocs, brewer's yeast and beer. Residues of XDE-729 methyl and XDE-729 acid in grain and all processed products from each of the three wheat and the three barley trials in treated as well as untreated samples were not detected (ND, <0.003 mg/kg). These studies demonstrated that residues of XDE-729 methyl are not expected to concentrate in processed fractions of grain.

2.4.2.6 Livestock feeding studies

Based on residue trials conducted in the EU according to the critical GAP and resulting residues in cereal grain and straw, intake of XDE-729 methyl and XDE-729 acid in the dairy cattle diet is a maximum 0.021 mg/kg on a dry matter (DM) basis (0.0008 mg/kg bw/day). Although residues from uses proposed in the EU do not result in sufficient dietary burden to trigger the requirement for a cattle feeding study, a study was conducted to support uses in other regions of the world where the dietary burden is greater, due primarily to the potential for use of cereals as forage and hay with short PHIs.

Animals were orally dosed for 28 or 29 consecutive days with a compound feed containing the test item, XDE-729 methyl. In the cattle feeding study, cows were divided into 4 separate treatment groups / dose levels. (Control, 0x, 1x, 3.1x and 15.6x). Based on dose levels of XDE-729 methyl administered along with actual feed consumption levels during the period of dosing, the average dose levels of XDE-729 methyl expressed as concentrations in the diet of treated cattle on a dry weight basis were: 1.06 mg/kg (1x), 3.16 mg/kg (3.1x) and 15.31 mg/kg (15.6x). Results showed that residues of XDE-729 methyl and XDE-729 acid above the LOQ do not transfer into whole milk, skim milk, cream, muscle, liver, kidney, subcutaneous fat, mesenteric fat or perirenal fat at any of the dose levels. Residues of the metabolite X11449757 above the LOQ do not transfer into whole milk, skim milk, cream, muscle, subcutaneous fat, mesenteric fat or perirenal fat, with the exception of a single residue of 0.012 mg/kg in mesenteric fat and a single residue of 0.014 mg/kg in perirenal fat from cows in the highest (15.6x) dose level group. Residues of X11449757 above the LOQ transfer into liver at the 1x, 3.1x and 15.6x dose levels and into kidney at the 3.1x and 15.6x dose levels. Although levels of X11449757 were monitored in milk and tissues, X11449757 is not proposed for inclusion in the residue definition in livestock. Depuration data generated using the 12 cows in the 15.6x (15.31 mg/kg) dose level showed that residues of X11449757 declined rapidly in liver and kidney following withdrawal of the test items from the cows' diet. All residues were below the LOQ by Day 31 of the study (3 days of depuration) and at that time, except for liver from one cow with a detectable residue that was <LOQ (residue of 0.004 mg/kg), all other residue values were ND (<0.003 mg/kg).

To conclude, results from the goat (ruminant) metabolism study with XDE-729 methyl suggest that no quantifiable residues of XDE-729 methyl or XDE-729 acid would be present in milk or edible tissues when dietary intake of XDE-729 methyl is 0.035 mg/kg or less in feed. Data from the lactating ruminant feeding study shown above provide further evaluation of the potential transfer of XDE-729 methyl residues from the diet of dairy or beef cattle to milk and edible tissues. The lowest dose level evaluated in that study was equivalent to XDE-729 methyl at 1.06 mg/kg feed on a DM (dry matter) basis or 0.037 mg/kg bw/day, if expressed on the basis of bodyweight. At this dose level, residues of XDE-729 methyl and XDE-729 acid in milk, muscle, fat and liver were not detected (ND, <0.003 mg/kg). In kidney, in one cow the residue of XDE-729 acid was <0.01 mg/kg and in the other three cows was not detected (ND, <0.003 mg/kg). The lowest dose level used in the cattle feeding study was 22N or 46N greater than the maximum expected dietary intake of residues in beef or dairy cattle, respectively (0.037 mg/kg bw/day / 0.0017 mg/kg bw/day = 22, or 0.037 mg/kg bw/day / 0.0008 mg/kg bw/day = 46). Based on these results residues of XDE-729 methyl or XDE-729 acid in milk or edible tissues are not expected to be detectable (ND, <0.003 mg/kg) based on dietary intake of residues resulting from the proposed uses of XDE-729 methyl in cereals.

Based on feed commodities considered in this submission, only cereal grain is a potential contributor to residues in the poultry diet. Since residues of XDE-729 methyl and XDE-729 acid were ND (not-detected, <0.003 mg/kg) or <0.01 mg/kg in grain, dietary intake of residues in poultry is expected to be insignificant. Results from the poultry NOR / metabolism study presented above along with the insignificant dietary intake of residues from grain indicates that residues in poultry commodities would be expected to be non-detectable (<0.003 mg/kg). Therefore, no poultry feeding study was required.

Metabolism of XDE-729 methyl in ruminants (goats) is similar to the metabolism observed in rodents (rats), the feeding study conducted with dairy cattle may be extrapolated to pigs and swine. However, due to the very low level of potential dietary intake of residues in pigs (grain residues <0.01 mg/kg) there is no requirement for feeding study results for pigs and residues in edible tissues of pigs are expected to be far below the LOQ of 0.01 mg/kg.

2.4.2.7 Residues in succeeding or rotational crops

Based on results from the confined rotational crop study, which indicated a very low potential for residues in succeeding crops, no field residue trials with succeeding crops are expected to be necessary.

2.4.2.8 Estimates of potential and actual dietary exposure through diet and other means.

UK and EU chronic and acute consumer risk assessments (UK NEDI, NESTI and EU PRIMo) have been performed using appropriate residue endpoints (chronic: STMR; acute: HR) which were derived from supervised residue trials that support the proposed GAP. It is noted that since residues in grain at harvest are <LOQ, the NEDIs determined above will be the same as the TMDIs, and the MRL has been taken account of since it is the same as the HR.

Chronic intakes for all consumer groups are below the proposed ADI of 0.058 mg/kg bw/day and therefore no health effects are expected.

Acute intakes for all consumer groups are below the proposed ARfD of 2.5 mg/kg bw/day and therefore no health effects are expected.

2.4.3 Residues relevant to worker safety

See Section 2.3.6.1 above.

2.4.4 Proposed EU MRL's and compliance with existing MRL's

Based on the proposed residue definition along with results from crop residue trials, MRLs are proposed. The RMS note that EU MRLs are not currently required for commodities used as livestock feed; however, in this case estimated MRLs for straw have been presented in the tables above (under the heading residues from supervised trials) for information only, with a view to when MRLs will be set for animal feed commodities in future. Residues of XDE-729 methyl (sum of residues of XDE-729 methyl and XDE-729 acid expressed as XDE-729 methyl equivalents) in grain in winter wheat, spring wheat, winter barley and spring barley trials were not detected (<0.003 mg/kg) or were less than the LOQ (<0.01 mg/kg). Consequently, the calculated MRL in each case was 0.02 mg/kg (the residue definition for both risk assessment and enforcement is XDE-729 methyl ester and XDE-729 acid. The residue level is the sum of the two components in the residue definition). Since the straw for winter barley had somewhat higher residues than in the other cereal crops, it is anticipated that in future the proposed MRL for XDE-729 methyl in cereal straw will be based on winter barley and then proposed by extrapolation for the other cereals on which use is requested. For consistency, it is proposed that the MRL for XDE-729 methyl in grain be based on that for winter barley and then established in the other cereal grains also at 0.02 mg/kg by extrapolation. **Therefore, a MRL for XDE-729 methyl of 0.02 mg/kg is proposed for the following cereal grains: barley (including spring and winter barley) and by extrapolation wheat, to include spring wheat, winter wheat, soft wheat, durum wheat, triticale and spelt), and rye.**

No MRL's are proposed for food commodities from livestock since dietary intake of residues in ruminants, poultry and swine is insignificant (<0.01 mg/kg) and

secondary residues of XDE-729 methyl and XDE-729 acid in commodities from these animals are expected to be non-detectable (ND).

Residues of cloquintocet mexyl and cloquintocet acid in grain and straw in these trials were ND (<0.003 mg/kg) and are within levels previously evaluated for other approved uses of cloquintocet mexyl in the EU and therefore do not require further evaluation. Since cloquintocet-mexyl is safener rather than an active substance, no MRLs are established.

2.4.5 Proposed EU import tolerances and compliance with existing MRL's

No EU import tolerances are requested at this time.

2.4.6 Basis for differences, if any, in conclusions reached having regard to established or proposed CAC MRL's

There are no CODEX MRL's in place so this is not relevant.

2.5 Fate and behaviour in the environment

2.5.1 Definition of the residues relevant to the environment

The residue definition for further risk assessment is defined as follows:

In soil, parent XDE-729 methyl, X11393729 and X11449757

In surface water, parent XDE-729 methyl, X11393729, X11406790, X11449757, and aqueous photolysis metabolites Deg 10, Deg11 and Deg 14

In sediment, parent XDE-729 methyl, X11393729, X11406790 and X11449757, and aqueous photolysis metabolites Deg 10, Deg11 and Deg 14

In groundwater, parent XDE-729 methyl, X11393729 and X11449757

In air, parent XDE-729 methyl

2.5.2 Fate and behaviour in soil

Route of degradation – aerobic soil

A study was conducted to investigate aerobic route of degradation of XDE-729 methyl on four soils. A similar study was also conducted on sterile samples of the same soils. In general the soils were considered to represent an appropriate range of soil properties, possessing a range of pH from moderately acid to weakly basic. Initial microbial content in three of the four soils appeared to be less than 1% of the organic carbon content, but the RMS does not consider this to be an unacceptable

deviation from the OECD 307 study guideline. Whilst three of the four soils had a lower microbial biomass than the 1% of total organic carbon recommended by the OECD 307 guideline, the acceptability of the microbial viability of these soils could also be partially inferred from the different behaviour observed in the truly sterile soils, particularly in relation to the degradation of the metabolite X11393729. Study temperature and moisture conditions were 20°C and 50% of MHC. The study was conducted in the dark. Acceptable mass balances were obtained in all four soils.

Extraction procedures appear to have been designed to extract as much radioactivity as possible without adversely altering the identity of the substances extracted. Given the instability of the parent under moderately acid and alkaline conditions, the Applicant found that more commonly used extraction strategies resulted in hydrolysis of extracted substances and/or loss of radioactivity. This explains the use of the accelerated solvent extraction, and this is considered to be reasonable. However, in spite of the efforts to obtain a method capable of extracting the residue without changing its nature, XDE-729 methyl still formed high levels of unextracted residues, even with exhaustive extraction techniques. In practice, the Uniform Principles criteria of *'no authorisation where.....during laboratory tests, form non-extractable residues in amounts exceeding 70% of the initial dose after 100 days with a mineralisation rate of less than 5% in 100 days.....'* are met in the RefSol 03-G soil where the incubation with pyridine-labelled XDE-729 methyl reached 73.8% AR unextracted residue with 3.3% mineralisation. Two of the other soils also exceeded 70% unextracted residues during the study but also had greater than 5% mineralisation and thus do not officially meet the strict Uniform Principles criteria. Nevertheless, the RMS considers that the effects of possible accumulation of unextracted residue must be addressed as specified by the Uniform Principles.

With this in mind, the applicant conducted a kinetic assessment to obtain degradation parameters for unextracted residues formed in the aerobic route and rate of degradation study. The modelling generally appeared to be acceptable although it must be borne in mind that formation and turn-over of soil organic matter generally tends to be a long-term process. The maximum duration of the study was 153 days. Thus there may be significant uncertainty over the accuracy of the predictions as the unextracted residue levels at study end were either still increasing or only experiencing a small decline; optimised parameters often showed relatively high standard deviation and at times confidence intervals including zero and resulting DT50 parameters were extrapolated well beyond the study duration. However in most cases the total extractable residue had fallen below 10% AR by study end. With these caveats in mind, the modelling predicted the extractable residue to decline biphasically and there was reasonable visual simulation of the unextracted residue using FOMC kinetics for the extractable residue followed in sequence by SFO kinetics for the unextracted residue. Applying the predicted formation and decline of unextracted residues to a simulation of annual applications of XDE-729 methyl, the maximum accumulation was predicted to be 0.87 - 3.83 times the initial parent residue (on a molar basis). The PY label predicted greater accumulation than the PH label. Maximum accumulation was predicted within 10-15 years for the PY label and 5-10 years for

the PH label. Given that there is much uncertainty over the extent of accumulation, the RMS considers that the maximum accumulation factor of 3.83x the initial parent dose should be used for risk assessment purposes. However, it must be borne in mind that even using the highest accumulation factor may not necessarily reflect highest levels of accumulation and the extent of. It should be noted that the Applicant also conducted a separate study investigating formation of unextracted residues in two soils to support a study to test the effect of unextracted residues on earthworms. This generally noted lower levels of unextracted residues than seen in the standard route and rate of degradation studies, however, reasonable levels of unextracted residues had developed by approximately 30 days after treatment, i.e. the time at which earthworms were introduced into the effects study. An assessment of possible accumulation of unextracted residues is presented in section B.8.3.

As stated above, XDE-729 methyl gave rise to relatively high levels of unextracted residue in microbially active soils. Generally, the pyridine ring-labelled material tended to give higher levels of unextracted residues; with 62.5 – 82.5% AR at 104 DAT; the phenyl ring-labelled material gave 59.5 – 64.4% AR as unextracted at 104 DAT. However, mineralisation was moderate with 1.8 – 17.3% AR as CO₂ at 104 DAT with the phenyl ring-labelled material and 3.3 – 21.0% AR at 104 days with the pyridine ring-labelled material. Mineralisation would suggest that the molecule is undergoing significant degradation, as would the presence of polar and 'other' material. In particular, the RefSol 03-G soil which met the Uniform Principles unextracted residue/mineralisation criteria, showed up to 4.4% polar material and up to 7.2% of 'other' comprising a number of unidentified components, none of which exceeded 5% AR. Again, this suggests that significant degradation is occurring to the a.s. and its primary metabolites in microbially active soils rather than unchanged or relatively unchanged substance being incorporated into soil as unextracted residue. In the sterile soils, much lower levels of mineralisation and formation of unextracted residues were seen at equivalent sample times, suggesting that microbial activity is responsible for degradation of the active substance and metabolites and incorporation of the radiolabelled residue into unextracted residues. Results of the sterile incubations also suggest that there was a slowing of the degradation of XDE-729 methyl, although it was still relatively rapid (non-sterile soil DT50 values in the range of 1 – 2 days and DT90 values in the range 4 – 16 days; sterile soil DT50 in the range 7-12 days and DT90 values in the range 22-75 days. This suggests that microbial activity is involved in degradation of XDE-729 methyl, but abiotic processes are also likely to be involved. The magnitude of degradation rates seen in the hydrolysis study (section B.8.4.1) suggests that simple hydrolysis may not be the dominant abiotic process, but that there may be some form of catalysed process occurring to maintain the relatively rapid degradation of the a.s. in the absence of an active microbial population. In addition, the sterile incubations demonstrate that degradation of X11393729 is clearly microbially mediated, with an accumulation of residues of this metabolite at high levels at the end of the study in sterile incubations, as opposed to rapid formation followed by relatively fast decline under non-sterile conditions. This would further support the theory that the formation of unextracted residues following application of XDE-729 methyl is due to microbial degradation processes.

The Applicant also conducted a further study on two soils to explore formation of unextracted residues. This was to support Ecotoxicological testing intended to assess the effects of accumulated unextracted residues on earthworms. Both soils, similar to two soils used in the standards route and rate of degradation study, were dosed with three different concentrations of Py-labelled XDE-729 methyl. The study lasted for 89 days. At this time, levels of unextracted residues had increased to 67.8 – 81.7% AR

Three metabolites were positively identified. The primary metabolite, X11393729, is the demethylated carboxylic acid metabolite and can be thought of as the acid formed by hydrolysis of the ester bond; the methyl group is lost from the pyridine ring. High levels were formed relatively quickly, maximum levels being 38.2 – 72.7 % AR at 3 - 7 DAT. The subsequent study in sterile samples of the same soils demonstrated slower transformation of XDE-729 methyl to the acid suggesting that although an abiotic process was capable of forming the acid, microbial degradation is still likely to be significant in the formation of the acid. The sterile incubations also demonstrated that microbial degradation is also likely to be responsible for degradation of X11393729 as its concentrations had not apparently peaked during the 62 day sterile incubation in all four soils, whereas concentrations had markedly declined by this point in the microbially active incubations.

The secondary metabolite in terms of concentration was X11449757 which reached 2.7 – 17.4 % AR at 3 - 14 DAT. Generally the peak of formation of X11449757 was one sample time after the peak of X11393729 formation suggesting relatively rapid formation of X11449757 from X11393729. X11449757 appears to be formed from X11393729 by loss of the methyl group associated with the phenyl ring, forming a hydroxyl group.

A further metabolite, X11406790, was also identified, but the maximum amount seen was 1.4% AR at 3 DAT. It is considered by the RMS that this metabolite does not need any further consideration in environmental exposure assessment for soil or groundwater. However, both X11393729 and X11449757 must be included in environmental exposure assessment for soil and groundwater. X11406790 appears to be formed from XDE-729 methyl by loss of the methyl group associated with the phenyl ring, forming a hydroxyl group.

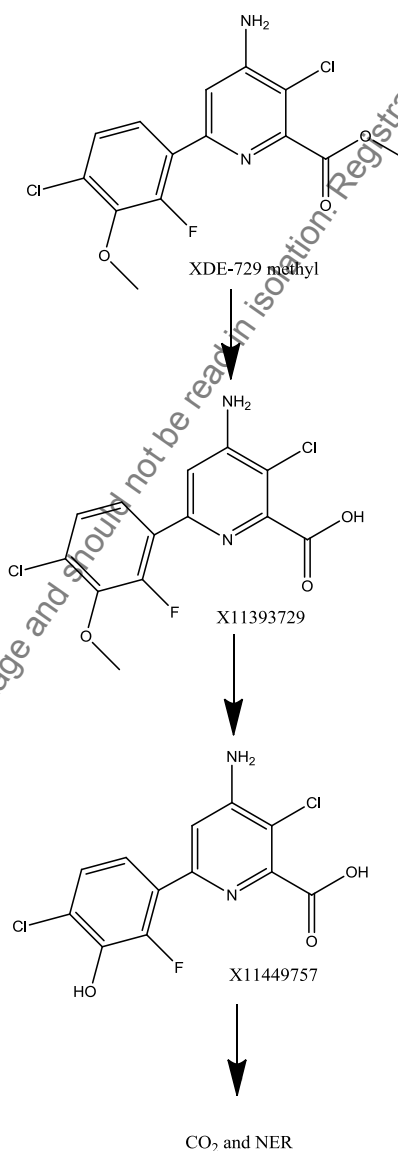
Relatively low levels of polar material (presumably eluting very quickly from the HPLC column at the solvent front) and 'others' (unidentified components, none of which individually formed 5% AR at any one time) were formed during the incubations.

An incubation at 10°C was also conducted in a single soil. The same pattern of metabolite formation was seen at the lower temperature compared to the 20°C incubation, but degradation and formation processes appeared to be slowed down as might be expected. Parent degradation rate appeared to be 2x that at 20°C; the top down DisT50 for X11393729 was approx 2.8x longer than at 20°C.

The proposed metabolic pathway of XDE-729 methyl under dark, aerobic soil conditions is presented below.

The RMS considers that the metabolites X11393729 and X11449757 should be included in environmental exposure assessment for soil, groundwater and surface water/sediment (as soil metabolites potentially reaching surface water).

Proposed metabolic pathway of XDE-729 methyl under dark, aerobic soil conditions



Route of degradation – anaerobic soil

A study investigating the anaerobic route of degradation of XDE-729 methyl in four soils was conducted. Study conduct was generally appropriate and was of a similar design to the aerobic studies described above. The study was conducted

with a two day aerobic period, corresponding to approximately one half-life, before flooding and purging with nitrogen to initiate anaerobic conditions. This is in-line with the OECD 307 study guideline and is thus appropriate. Reference to redox potential and dissolved oxygen content in the incubations suggest that anaerobic conditions developed over time post-flooding of the soils.

The use of the same four soils as in the aerobic study allows a good comparison of behaviour under anaerobic and aerobic conditions. The extent of both mineralisation and formation of unextracted residues were significantly reduced under anaerobic conditions, and there was relatively little difference between radiolabels. The maximum mineralisation and unextracted residues under anaerobic conditions were 0.8% AR and 48.6% AR respectively after 100 days. This compares to maxima of 21% mineralisation and 82.5% AR unextracted residue at 100 DAT in the aerobic study.

The profile of degradation was very similar for XDE-729 methyl, and it is possible that the majority of degradation had taken place before the establishment of truly anaerobic conditions had taken place. However, it still appears that degradation of XDE-729 methyl to form X11393729 was largely unaffected by imposition of anaerobic conditions; degradation rates calculated from the day of flooding ranged from DT50s of 0.9 – 2.8 days with DT90s of 3.1 – 29 days. The first degradation product appears to be X11393729 which apparently underwent slower degradation under anaerobic conditions but was still degraded to an appreciable extent; SFO top down DT50s range from 21 – 100 days. However, there were clear indications that metabolite X11449757 exhibited much slower degradation with accumulation to levels of up to 54.3% at or close to the end of the study (120 days); it was not possible to calculate top down degradation rates for this metabolite due to no or insufficient decline by the end of the study suggesting potential persistence under anaerobic conditions. However, the RMS considers that under the majority of agricultural conditions, the imposition of anaerobic conditions so soon after treatment and for such an extended time is unlikely and that in practice, accumulation of X11449757 to such high levels is unlikely. A further metabolite, X11406790, was only seen at levels <3% AR with these highest levels occurring at or soon after flooding and were probably associated with formation under aerobic conditions. The route of degradation of XDE-729 methyl under anaerobic conditions is essentially the same as that proposed under aerobic conditions. It was also noted that over the course of the study, there was significant partitioning of radioactivity out of the soil and into the water, such that the maximum amount of radioactivity in the water ranged from 29 – 54% AR.

Route of degradation – soil photolysis

A soil photolysis study was performed on a single soil; this soil had also been used in the aerobic and anaerobic soil studies. Moist soils were incubated for 15 days at 28°C with continuous exposure to a xenon lamp, equivalent to 28 days summer sunlight at 40°N. The lamp was appropriately filtered to exclude wavelength <290nm. In this study, it was apparent that both XDE-729 methyl and X11393729 degraded more slowly under irradiated conditions than under the dark control conditions, particularly from 4 DAT onwards. The wording of the study suggests

that the dark control samples were supplied with moistened air, but this was not stated to be the case with the irradiated samples. It is possible that under the bright artificial light conditions in the irradiated samples that the soil may have been subject to drying and this may have resulted in the differences in a.s. concentration from 4 DAT. Given the apparent influence of both microbial and abiotic factors in the degradation of the a.s., drier conditions could have inhibited these processes. Thus, under the conditions of the study, there was a very limited influence of photolytic processes on degradation compared to aerobic processes. However, this finding is in sharp contrast to the potential influence of photolysis in aquatic systems (see section B.8.4.2).

The identified metabolites were those found in both aerobic and anaerobic studies, and there was no indication of any photolysis specific metabolites being formed. Metabolite formation was greater in the dark control compared to the illuminated and this is most likely to be related to the same conditions which limited degradation of the parent in the irradiated samples. The route of soil photolytic degradation is postulated to be the same as that under aerobic soil conditions.

Rate of degradation – aerobic soil

An additional report was submitted calculating degradation rates of XDE-729 methyl and its two main soil metabolites requiring environmental exposure assessment from the aerobic soil route and rate of degradation study. The study was conducted to obtain modelling endpoints according to FOCUS Degradation Kinetics guidance, but was also considered appropriate to obtain persistence endpoints for these substances.

XDE-729 methyl was found to degrade very rapidly at 20°C and optimum moisture content with DT50 values in the range of 1 – 2 days and DT90 values in the range 4 – 16 days. The first metabolite to be formed, X11393729, was also generally rapidly degraded, with decline DT50 from the peak observed concentrations ranging from 3 – 36 days and DT90s of 11 – 119 days. The other metabolite, X11449757, appeared to decline more slowly, with decline DT50 from peak observed in the range 25 – 77 days with DT90s of 106 – 255 days.

The longest decline rates for all three substances were observed on one soil (Yolo). There appeared to be no particularly extreme characteristics of this soil that would suggest any reason why degradation may have been slower on this soil, and this may just reflect natural variation in capability of soils to degrade these substances.

Following consideration of the physical/chemical properties of the parent and two main aerobic metabolites, particularly the pKa values and solubilities, and investigating potential correlations between DT50 and soil properties, the RMS considers that pH dependent degradation should be taken into account for X11393729 and X11449757 in environmental exposure modelling but not for XDE-729 methyl. For FOCUS modelling, short DT50 values should be used for acid pH and long DT50 should be used for alkaline pH. A further description of how the long pH has been taken into account in groundwater modelling is given in section B.8.6.2.

The magnitude of the DT50 and DT90 values for XDE-729 methyl do not trigger field dissipation studies. One DT50 value for X11449757 exceeds the DT50 of 60 days which triggers field dissipation studies for parent substances. However, the Applicant has submitted European field dissipation studies anyway.

Persistence and modelling endpoints from laboratory incubations are reproduced below.

Laboratory soil persistence endpoints for XDE-729 methyl and its soil metabolites (values in parentheses for RefSol 03-G soil are moisture corrected)

	XDE-729 methyl	X11393729	X11449757
Yolo			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	1.8 d	35.9 d	76.7 d
DT90	16.3 d	119 d	255 d
χ^2	3.3	6.0	5.2
RefSol 03-G			
Kinetics	SFO	Top down SFO	Top down SFO
DT50	1.3 d (1.1 d)	3.3 d (2.7 d)	25.1 d (20.4 d)
DT90	4.5 d (3.7 d)	11 d (9.0 d)	84 d (68.4 d)
χ^2	8.4	20.1	17.0
Site E			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	1.1 d	7.6 d	31.8 d
DT90	6.1 d	25.4 d	106 d
χ^2	4.4	13.1	13.8
Site I2			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	0.9 d	13.6 d	47.7 d
DT90	3.8 d	45.2 d	158.5 d
χ^2	7.0	11.3	12.3
Worst case			
DT50	1.8 d	35.9 d	76.7 d
DT90	16.3 d	119 d	255 d

Soil modelling endpoints for XDE-729 methyl and its soil metabolites (values in parentheses for RefSol 03-G soil are moisture corrected)

	XDE-729 methyl	X11393729	X11449757
Yolo			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	2.4 d (2.0 d)	28.7 d	76.7
DT90	8.1 d (6.7 d)	95 d	255
Formation fraction	-	0.6372	1**
χ^2	12.5 (18.3)	16.4	5.2
RefSol 03-G			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.3 d (1.1 d)	2.0 d (1.6 d)	25.1 (20.4 d)
DT90	4.5 d (3.7 d)	6.8 d (5.5 d)	84 (68.4 d)
Formation fraction	-	0.8548	1**
χ^2	8.4	14.4	17.0
Site E			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.3 d (1.2 d)	4.7 d	31.8
DT90	4.2 d (4.0 d)	15.8 d	106
Formation fraction	-	0.7733	1**
χ^2	13.3 (10.9)	14.4	13.8
Site I2			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.0 d (0.9 d)	11.7 d	47.7
DT90	3.3 d (3.0 d)	38.9 d	158.5
Formation fraction	-	0.7753	1**
χ^2	8.0 (8.3)	14.7	12.3
Geometric mean			
DT50	1.4 d (1.3 d)	7.5 d	41.3 d (39.4 d****)
Formation fraction*	-	0.7602	1

*Arithmetic mean **Worst case assumption using top down DT50 values

***omitting Site I2 value from geometric mean

Field dissipation studies

It is noted that whilst the results of the aerobic soil degradation studies in soil indicate XDE-729 methyl does not trigger field studies under data requirements for Directive 91/414/EEC, the Applicant chose to provide field dissipation studies. The studies were all conducted at the same sites (Germany, UK, Spain and France) but with spring and autumn applications investigated separately, presumably as the intended GAP may recommend either autumn or spring applications. In general the studies were considered to be acceptable with appropriate sampling numbers and sampling depth, on-site weather recording as well as measurement of soil temperature and moisture. The studies were on bare soil plots and were of approximately one year duration. Analysis was made for XDE-729 methyl,

X11393729 and X11449757. The method of analysis was virtually identical to that employed in the laboratory soil studies. Given the low application dose (up to 8 g a.s./ha), the method had a suitably low LOQ of 0.05 µg/kg which was able to quantify well below 10% of the parent; in relation to the lowest peak average residue across the three replicate plots recorded at the France Autumn applied study, the LOQ equated to 1.6% of the parent dose, but at other sites was usually around or below 1% of the parent dose. Procedural recovery information suggested that recoveries could vary quite widely, particularly for metabolites. However, in general, the ranges appeared reasonable in comparison with EU guidance on methods of analysis for pre-registration studies. There were some instances of very high or very low procedural recoveries, but the RMS does not consider that these are sufficient to invalidate the studies.

Residues were generally detected down to a maximum depth of 30cm, thus there was no regular sampling below this depth. The RMS considers this to be acceptable and a scrutiny of the residues in the lowest analysed layers suggests that residues were generally less than 1% of the average peak residue of the parent at each specific trial site. This suggests to the RMS that there were no significant leaching losses below the lowest depth of sampling.

Generally, XDE-729 methyl was observed to dissipate at a slower rate compared to that seen in the laboratory. With the exception of the Spanish site, dissipation appeared to be faster when applications were made in the autumn. A biphasic pattern was often apparent with a pronounced 'tail' often occurring around 90% dissipation of the parent. However, it was also apparent that at every site, by the time the first sample after treatment was taken, there had been appreciable degradation of the parent given the marked residues of X11393729 and sometime X11449757 at 0 DAA. In calculating the true time 0 residue for the purposes of calculating dissipation rates under ambient conditions, the metabolite residues were added to the parent residues but not corrected for molecular weight difference. The RMS considers that this is acceptable in this case as both metabolites are not that different in molecular weight to the parent. In any case, molecular weight correct would lead to slightly higher initial parent residues which tends to have the effect of shortening the parent dissipation rate. The RMS interpretation of the kinetic fitting for the parent under ambient weather conditions suggests a range of DT50 values from 2.1 – 43 days with DT90 values 49 – 144 days; these values are from a SFO, FOMC and DFOP kinetics. The longest DT50/DT90 combination was 43 days/144 days with SFO kinetics at the UK Spring site. This combination is proposed for use in simple PECsoil calculation procedures.

As noted above, metabolites X11393729 and X11449757 were frequently observed. Using the mean replicate residues and correcting for molecular weight, X11393729 was seen at maximum observed molar formation of 6.5 – 40.1%. The time of occurrence of these residues was variable, occurring at 0 – 89 DAT. These levels of formation were typically lower than seen in laboratory aerobic soil tests. For X11449757, maximum observed molar formation was 1.8 – 13.8% at 0 – 180 DAT. Observed formation was typically within the range of that seen in laboratory aerobic soils.

Whilst sequential parent/metabolite modelling of kinetic parameters was challenging in terms of obtaining robust parameters, both metabolites typically showed decline phases. Based on calculation of top down SFO kinetics, X11393729 had dissipation DT50 ranging from 17 – 264 days, with two of the DT90s being longer than 1 year. Thus a consideration of potential accumulation of X11393729 should be undertaken.

Also based on calculation of top down SFO kinetics, X11449757 had dissipation DT50 ranging from 87 – 197 days, with four of the DT90s being longer than 1 year. Thus a consideration of potential accumulation of X11449757 should also be undertaken.

In terms of generating modelling parameters from the field dissipation studies, the Applicant undertook a temperature and moisture timestep normalisation procedure. The Applicant considered that the studies were suitable for normalising as they considered that there the data described degradation rather than encompassing other dissipation processes such as volatilisation, plant uptake or leaching. The RMS evaluated the cases presented and agrees with this assessment for XDE-729 methyl, X11393729 and X11449757.

In undertaking the assessment for parent XDE-729 methyl, following discussions with the RMS, the Applicant attempted to take into account the EFSA PPR Opinion from 2010 on obtaining DegT50 values from field dissipation studies. In particular, this took into account the date by which 10mm rainfall had occurred following application. This is principally to eliminate the influence of surface processes such as soil photolysis or volatilisation. With hindsight, it is possible that the principles of the Opinion may not be that applicable to a substance such as this that tends to show relatively rapid degradation to an initial metabolite. Overall, the reasons for the apparently slower degradation seen in the field compared to laboratory conditions have not been elucidated. It is possible that the rapid decline phase seen in the field is consistent with hydrolysis to the acid metabolite, but it is possible that there may also have been an influence of photolysis as well. In addition, whilst the rapid degradation phase accounted for most of the disappearance of the parent, the presence of a distinct tail in the data at residues which tended to be greater than those seen in laboratory studies is not known. Therefore the RMS considers that it was still a reasonable request to make of the Applicant to conduct such an assessment.

SFO kinetics for parent were generated on complete datasets and following elimination of data before 10mm rainfall. In addition, flowcharts for application of DFOP and HS kinetics to the complete datasets were applied. In general, the DFOP and/or HS flowcharts tended to fail for one reason or another. The RMS observed that for the DFOP kinetic, the 'g' parameter was typically greater than 0.75 indicating that most of the residue was simulated to be in the fast phase compartment and with rapid degradation tending to dominate most of the residue decline. It is possible that this may have been due to relatively rapid hydrolysis of the parent methyl ester to the acid metabolite. Soil photolysis may have contributed to this, but given that degradation in the field was slower than in the laboratory, the RMS concludes that soil photolysis probably had only a minor role.

Overall, the RMS can agree to the use of these parameters calculated after 10mm rainfall as they ought to represent 'bulk soil matrix degradation'. The applicant eventually proposed to use SFO parameters for parent generated following elimination of data before 10mm rainfall. With this in mind, the recommended geometric mean SFO DT50 for use on exposure modelling using FOCUS groundwater and FOCUS surface water methodology is 20 days.

For the metabolites, it was noted that peak concentrations, particularly of X11393729, occurred relatively early after treatment. As noted above, applying DFOP kinetics to the parent generally resulted in high 'g' values as the fast phase of degradation tended to dominate the overall decline. If a process such as soil photolysis hastened the degradation of the parent, it is likely that the observed formation of metabolites may have been enhanced, and the Applicant proposed that it may be precautionary to use kinetic parameters from sequential modelling of parent and metabolites in exposure modelling provided that the rapid parent degradation was taken into account. Whilst the EFSA guidance of 2010 does not expressly detail how metabolites can be taken into account, the RMS can understand the Applicant's logic, particularly as there is a view that faster degradation of a precursor tends to lead to conservative formation of subsequent metabolites in exposure models. With this in mind, the Applicant derived separate endpoints for exposure modelling of parent alone, parent + X11393729 (for exposure concentrations of X11393729), and parent + X11393729 + X11449757 (for exposure concentrations of X11449757). It will be noted that in each step of modelling the calculated DegT50 values of precursors gets shorter, potentially increasing metabolite. This may be partly as the result of the use of IRLS weighting in the kinetic model which tends to result in better fitting of precursor substances than the more typical OLS weighting method. Thus the following parameters are proposed for FOCUS exposure modelling.

Kinetic endpoints for XDE-729 methyl exposure modelling (i.e. should not be used in exposure modelling simulating formation of subsequent metabolites)

Location	Season	Model	DT50 (d)	Chi ² Error (%)
Germany	Spring	SFO (after 10mm rain)	17	24
Germany	Autumn	SFO (after 10mm rain)	27	24
UK	Spring	SFO (after 10mm rain)	26	19
UK	Autumn	SFO (after 10mm rain)	8.2	20
Spain	Spring	SFO (after 10mm rain)	25	32
Spain	Autumn	SFO (after 10mm rain)	33	11
France	Spring	SFO (after 10mm rain)	17	15
France	Autumn	SFO (after 10mm rain)	19	19
Geomean			20	-
Average			22	-
Median			22	-

Kinetic endpoints for sequential exposure modelling of XDE-729 methyl and X11393729 (Acid), derivation of X11393729 PEC values only

Location	Season	Parent + Acid (SFO+SFO)					Top-down SFO	
		Parent DT50 (d)	Chi ² Err (%)	Acid DT50 (d)	FF	Chi ² Err (%)	Acid DT50 (d)	Chi ² Err (%)
Germany	Spring	0.7*	28	23	0.12	34	59	32
Germany	Autumn	2.5	32	42	0.44	25	30	13
UK	Spring	27	28	35	0.66	33	88	6.5
UK	Autumn	1.1	40	51	0.36	14	59	9.5
Spain	Spring	6.4	17	34	0.33	49	62	15
Spain	Autumn	9.1	20	40	0.34	49	85	16
France	Spring	6.6	40	2.3	1.00	49	29	25
France	Autumn	0.7	27	11	0.34	61	28	36
Geomean		3.3	-	22	0.38	-	50	-
Average		6.8	-	30	0.45	-	55	-
Median		4.5	-	35	0.35	-	59	-

FF = formation fraction

* DFOP/SFO model used

Kinetic endpoints for sequential exposure modelling of XDE-729 methyl, X11393729 (Acid) and X11449757 (X-757), derivation of X11449757 PEC values only

Location	Season	Parent + Acid + X-757 (SFO+SFO+ SFO)						Top-down SFO	
		Parent DT50	Acid DT50	Acid FF	X-757 DT50 (d)	X-757 FF	Chi ² Err (%)	X-757 DT50 (d)	Chi ² Err (%)
Germany	Spring	NC	NC	NC	NC	NC	NC	NC	NC
Germany	Autumn	1.9	43	0.41	8.9	1.00	16	76	4.6
UK	Spring	NC	NC	NC	NC	NC	NC	60	13
UK	Autumn	1.0	54	0.35	22	0.22	37	NC	NC
Spain	Spring	NC	NC	NC	NC	NC	NC	84	26
Spain	Autumn	NC	NC	NC	NC	NC	NC	60	12.6
France	Spring	5.8	1.9	1.00	73	0.18	36	107	21
France	Autumn	0.4	8.6	0.36	9.5	1.00	30	37	11
Geomean		1.7	14	0.48	19	0.45	-	67	-
Average		2.4	27	0.53	28	0.60	-	71	-
Median		1.5	26	0.39	16	0.61	-	68	-

FF = formation fraction NC = not calculated

The RMS notes that only three locations are represented for X11449757, which is acceptable for a metabolite. However, the RMS considers that the conduct of the studies under autumn and spring conditions and slightly different soil properties means that each site constitutes two separate results, i.e. there are four separate results for X11449757.

The RMS revisited the question of potential pH dependence of degradation. In the laboratory studies, the RMS considered that there appeared to be a trend towards increasing DT50 with increasing pH for both X11393729 and X11449757. In order to do this, the RMS considered the normalised SFO DT50 values in order to remove potential temperature and moisture interferences. The RMS considered both the top down and true metabolite degradation DT50 values. Making the assumption that normalisation should remove any differences from conducting studies in spring or autumn, the full data set of DT50s for each substance was used.

For parent, there was no consistent trend across the eight trials and the variation might be expected to be within natural variation. Therefore pH dependence is not taken into consideration.

For X11393729, there appeared to be a trend to increasing degradation rate with increasing pH with both top down and true degradation DT50 values, but this was not consistent across the eight trials. The lowest DT50 was at the lowest pH, but the highest DT50 was at just under pH7. In light of the apparent trend for pH dependency of degradation in the laboratory incubations, it is considered that pH dependence of degradation should be taken into account. However, whether this range would be considered to fall within that expected by virtue of natural variation could be the subject of an expert discussion.

For X11449757, top down DT50 varied from 37 – 107 days in the six sites it was calculated for. The maximum and minimum values in this range were at the Spain site with autumn and spring applications respectively, i.e. at very similar pH. There was no consistent trend in the top down or true degradation DT50s from the field studies for pH dependent degradation. The RMS does not consider that pH dependence of degradation should be taken into consideration for this metabolite given results under more realistic environmental conditions. However, the apparent discrepancy between the laboratory and field databases could be the subject of expert discussion as to whether pH dependence should be considered.

Thus, the RMS can accept the proposed geomean normalised field DT50 for exposure modelling purposes for XDE-729 methyl and X11449757, but proposes to use high and low DT50 values in each scenario for X11393729 to illustrate the influence of pH.

Adsorption, desorption and mobility in soil

A single study was performed to determine the soil adsorption characteristics of XDE-729 methyl and its soil metabolites X11393729 and X11449757. The study was generally performed appropriately to OECD 106 guidelines. Seven soils were selected with an appropriate range of soil properties including clay content and pH. It was noted that one of the seven soils tested was an organic soil ('Site M2') with a high organic carbon content (33.1%) which also possessed the lowest pH of the tested soils (pH 4.1). This inevitably led to high measured values of adsorption on this soil for each of the three tested substances. Whilst the OECD 106 guideline recommends use of a soil with >10% oc, it is considered that a soil with 33% oc cannot be considered to be typical of EU agricultural soils; the Jokioinen

FOCUS_{gw} scenario, considered to have a relatively high organic carbon content, has a maximum %OC content of 4%. It is thus considered that the choice of soil adsorption parameters for use in FOCUS modelling should exclude results from this soil.

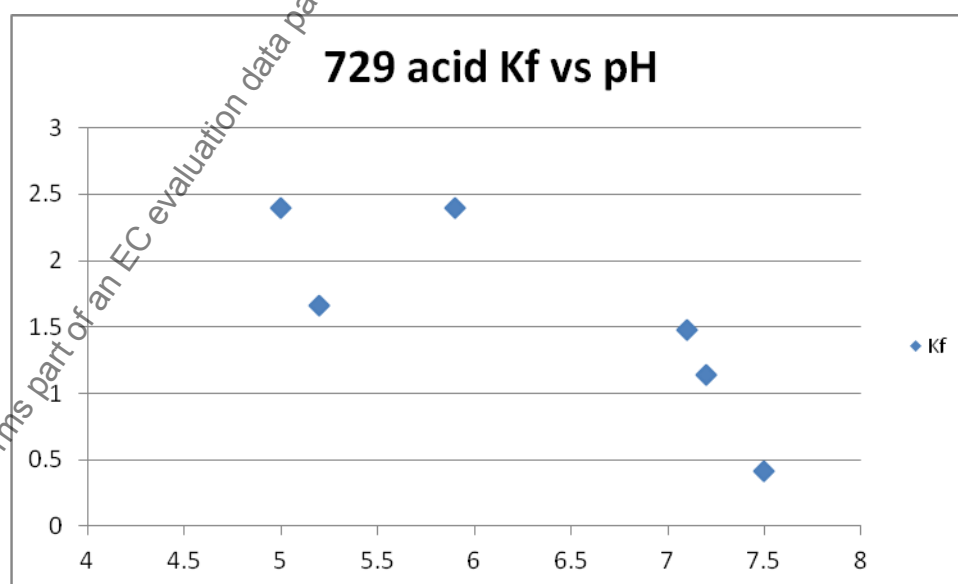
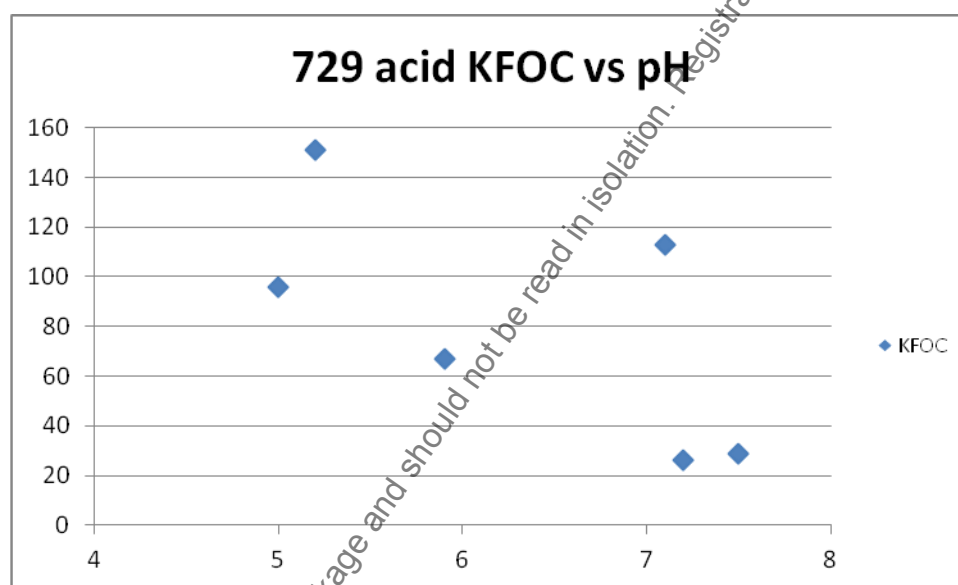
It must be borne in mind that XDE-729 methyl was unstable in the adsorption test, and whilst efforts were made to take this into account, this may have still impacted on the adsorption isotherms and increased uncertainty over their reliability relative to a more stable substance. The methodology used by the study authors of only analysing a single replicate for each dose and extrapolating the results to the other replicate is not ideal but the RMS can accept the specific case made by the Applicant as to the acceptability of this approach for XDE-729 methyl. In addition, the extrapolation of results at higher doses to those at lower doses is also not ideal, but is a consequence of the need to cover a concentration range of two orders of magnitude, the water solubility and the LOQ of the analytical method.

Given the uncertainty issues arising from degradation of XDE-729 methyl seen over the equilibrium time, the Applicant repeated the soil adsorption study for the parent with shorter equilibrium time of 2 – 6 hours. The same seven soils used in the first study were tested. The shortened equilibrium time was used in an attempt to retain as much undegraded parent in the test system as possible whilst allowing some opportunity for adsorption. Whilst not specifically stated, it appears that from the results of the preliminary test that there was an aim for 90% unchanged parent to remain in the system at the end of the equilibrium time. However, it is noted that during the incubations to establish Freundlich adsorption isotherms, total mass balance often fell below 90%; measurements of mineralisation or adsorption to experimental equipment were excluded from the mass balance assessment. A threshold mass balance of 84% was applied to the results and whether they could be used in the calculation of the Freundlich isotherm. The Applicant clarified that analysis of both replicates per dose in the adsorption isotherm test had been conducted as appropriate, i.e. where mass balance criteria for acceptance were met. Given that this meets the requirements of OECD 106, the RMS considers that the study can be accepted and that there is less uncertainty over the results given that both replicates were analysed and the extrapolation procedure between replicates employed in the first study was not practiced in this second study. Given that the reservations of the RMS over the first of the two soil adsorption studies on XDE-729 methyl in relation to the analysis procedure used, the RMS considers it better to use the results of the second study rather than the first as the definitive soil adsorption endpoints. This coincidentally leads to slightly more conservative adsorption values.

Considering the results of the second study and excluding the results of the Site M2 organic soil, the K_{foc} values of XDE-729 methyl in the repeated study range from 190 – 1812 ml/g and 1/n of 0.76 – 0.90. These K_{foc} values from the new study are slightly lower than from the original study and may simply reflect the reduced opportunity for undegraded parent to adsorb to soil particles as a result of the shortened equilibrium time. There does not appear to be a clear and consistent trend for dependence of K_{foc} on pH. In addition, there appears to be no consistent

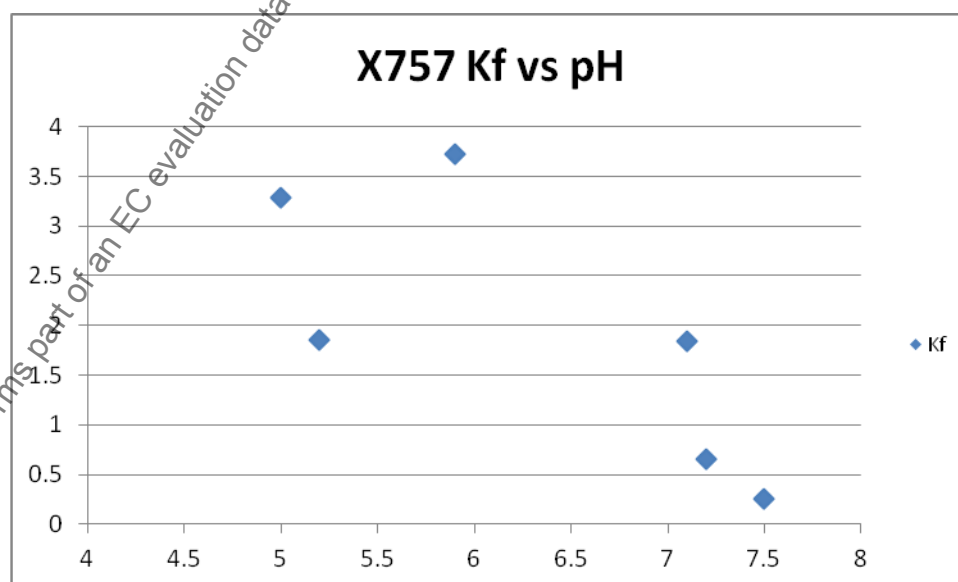
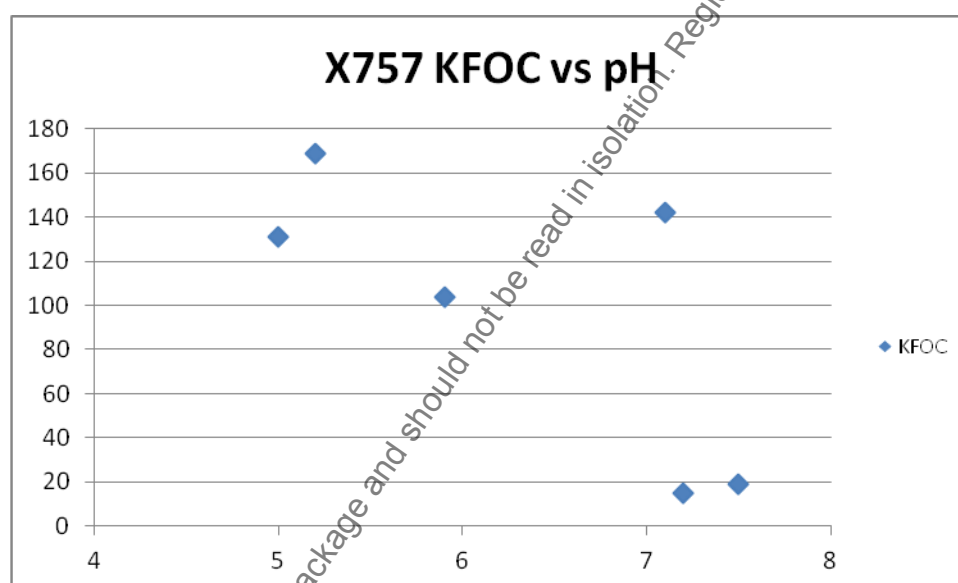
relationship between Kf and organic carbon content or Kf and pH. This suggests that that exposure modelling for parent ought to be conducted using both Kf and Kfoc.

Metabolite X11393729 demonstrated Kfoc values of 26 -151 mg/l and 1/n values of 0.83 – 0.96 following exclusion of the organic soil result. An exploration of Kf in relation to % organic carbon suggests that there is no convincing relationship of increasing adsorption with increasing organic carbon, which again suggests that Kf ought to also be explored as an input parameter for exposure modelling. Unlike the parent, there appears to be reasonably strong evidence that soil adsorption is related to pH, with stronger adsorption at low pH; this is the case for both Kfoc and Kf (see below). This might be expected due to a carboxylic acid group in X11393729 where lower pH would shift the equilibrium towards the undissociated form.



The possibility of pH dependent adsorption is supported by the pKa value of 5.11 for this substance (see section B.2 of the DAR). It is thus proposed that it is appropriate to take pH dependence into account in the environmental exposure assessment of X11393729.

Metabolite X11449757 demonstrated K_{foc} values of 15 - 169 mg/l and 1/n values of 0.83 – 0.95 following exclusion of the organic soil result. An exploration of K_f in relation to % organic carbon suggests that there is no convincing relationship of increasing adsorption with increasing organic carbon, which again suggests that K_f ought to also be explored as an input parameter for exposure modelling. As with X11393729, there appears to be reasonably strong evidence that soil adsorption is related to pH, with stronger adsorption at low pH; this is the case for both K_{foc} and K_f. This might be expected due to a carboxylic acid group in X11449757 where lower pH would shift the equilibrium towards the undissociated form.



The possibility of pH dependent adsorption is supported by the pKa value of 5.6 for the carboxylic acid group of this substance and 7.1 for the phenolic group this substance (see section B.2 of the DAR) It is thus proposed that it is appropriate to take pH dependence into account in the environmental exposure assessment of X11449757.

It should be noted that the Applicant has conducted exposure modelling using K_{foc} values for all substances included in risk assessment, and the need for exposure modelling using K_f for parent, X11393729 and X11449757 could be the subject of an expert discussion.

PEC_{soil} calculations were performed for XDE-729 methyl, X11393729 and X11449757. In addition, calculations of accumulation potential were conducted for unextracted residues as a result of application of XDE-729 methyl. These values have been used in ecotoxicological risk assessment. MS should note that these calculations assume a 70 day application interval for use on winter cereals. Consequently, MS should consider ensuring that a 70 day interval between applications is specified as a conditions of plant protection product authorisation.

2.5.3 Fate and behaviour in water

Aqueous hydrolysis

A study on the aqueous hydrolysis of XDE-729 methyl was submitted. The study was conducted under sterile conditions at pH 5, 7 and 9, and degradation at temperatures of 10, 25 and 50°C was investigated at each pH value. As might be expected, XDE-729 methyl degraded faster at higher temperatures. In addition, it exhibited clear pH dependence of degradation. The slowest degradation occurred at pH 7, faster degradation at pH 4 and fastest degradation at pH 9 (this would be consistent with acid and base catalysed ester hydrolysis). At 25°C, SFO DT50 values were 80.9 days at pH 4, 155 days at pH 7 and 3 days at pH 9. The magnitude of the degradation rates suggest that in the soil environment, abiotic hydrolysis is not solely responsible for degradation of XDE-729 methyl, but could be partially responsible. Metabolite X11393729 was the only identified metabolite which appeared to be stable in the study, tending to accumulate to a maximum at or towards the end of the study. The maximum accumulation was 99.6% AR at the penultimate time point at pH 9 and 50°C. The total of XDE-729 methyl and X11393729 accounted for the majority of radioactivity at each sample time, with less than 5% AR unidentified at any point.

Aqueous photolysis

Data on molar extinction of XDE-729 methyl indicate significant light absorbance at 290 nm (e.g. 3798 L mol⁻¹cm⁻¹), which suggests that the a.s. will be susceptible to aqueous photolysis.

An aqueous photolysis study was performed on XDE-729 methyl in both sterile pH 7 buffer and natural water. An artificial xenon light source appropriately filtered for wavelengths (cut-off 295nm) was utilised. XDE-729 methyl degraded extremely quickly under irradiated conditions with complete disappearance of the a.s. within 1 hour after the start of the study in both water systems. The SFO DT50

values were of the order of 4 minutes in buffer solution and 7 minutes in the natural water. Degradation was extensive with a very large number of radiolabelled components detected in both systems. As an example, in the buffer solution treated with phenyl-labelled material, up to 46 separate peaks, each of which comprised <1% AR, were seen in one replicate of the 7 DAT sample, and a total of 64 separate peaks were detected in this replicate in total. There was a trend for an increasing amount of radioactivity to be eluted at the solvent front during incubations; approximately 12- 40% AR was recorded in this region at or towards the study end in the irradiated incubations. This region was termed 'Deg 1' and is further discussed below.

Over the whole of the study, four separate metabolites were found to exceed 10% AR in individual replicates and could be allocated structures following LC/MS. These were: X11393729 accounting for 10.7% AR 10 minutes after treatment in natural water; Deg 10 accounting for 12.6 %AR 18 minutes after treatment in buffer solution; Deg 11 accounting for 15.7% AR 18 minutes after treatment in buffer solution; Deg 14 accounting for 11.5% AR 129 minutes after treatment in buffer solution. The RMS recommends that the four major aqueous photolysis metabolites should be subject to aquatic exposure and risk assessment. It was noted that Deg 10, Deg 11 and Deg 14 had all fallen below 10% AR within 4 hours of the start of the study, and thus appear to be transient.

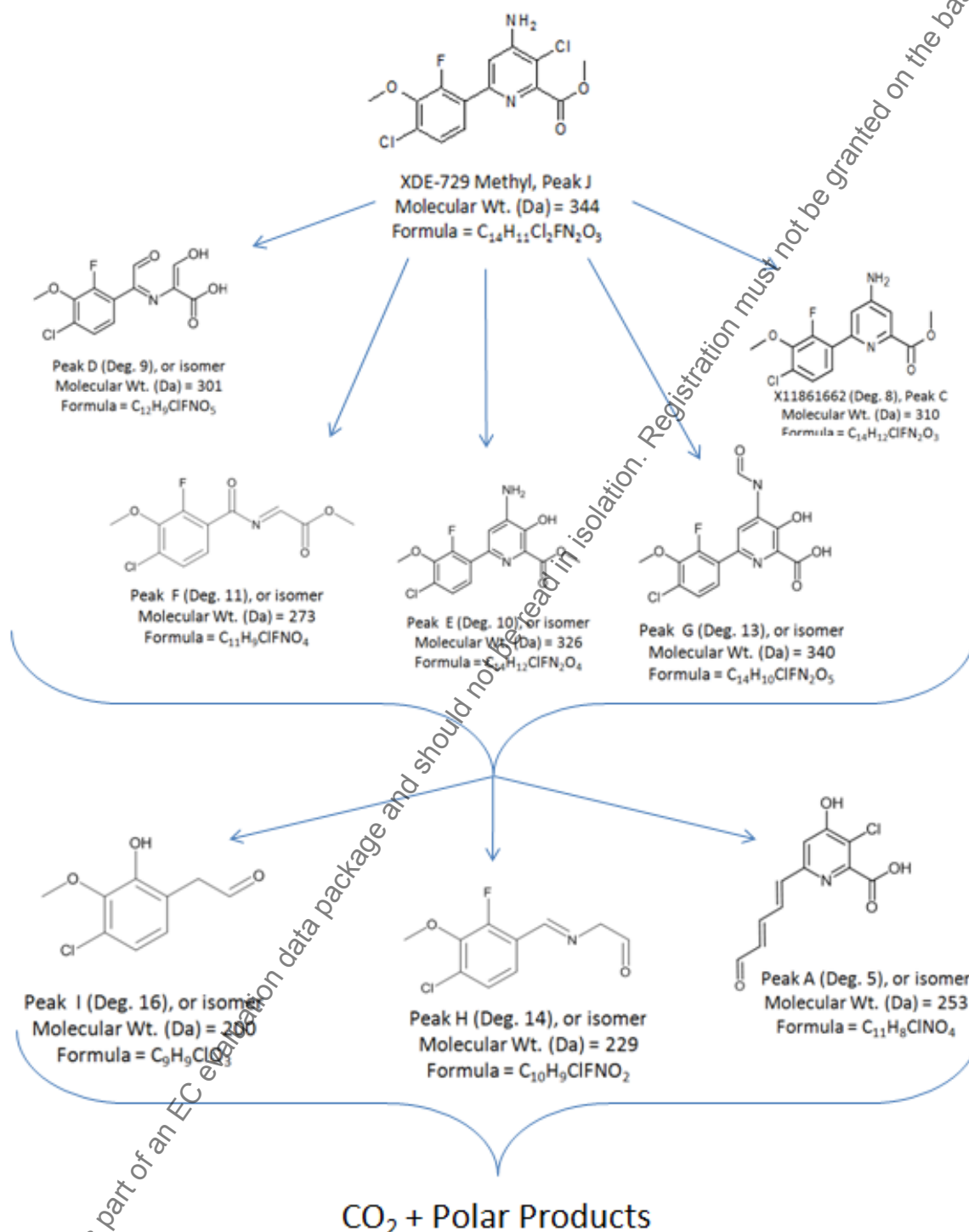
Three other chromatographic regions were detected which exceeded 10% AR, Deg 1, Deg 2 and Deg 4. These all eluted within 5 minutes of the HPLC run, and could not be detected by LC/MS suggesting that these regions did not contain any ionisable functional groups. Attempts to further characterise Deg 1 and Deg 2 failed to provide significant additional information, but Deg 4 was found to comprise a number of different components, none greater than 10% AR. Deg 1 and 2 are likely to also comprise radiolabelled fragments which could not be sufficiently retained by the HPLC columns used. Therefore, RMS considers that the chromatographic regions Deg 1, Deg 2 and Deg 4 do not require any additional risk assessment consideration.

Given the results of the aqueous photolysis study, the RMS considers it very likely that XDE-729 methyl will undergo photolysis in natural waters following exposure via spray drift. Given the apparent susceptibility of the a.s. to photolytic processes, it is possible that photo-degradation could also contribute to degradation were the a.s. to enter surface water via run-off or drainflow events. However, the RMS considers that in reality this is unlikely as drainage or run-off water containing residues of XDE-729 methyl is likely to be relatively turbid and reduce the propensity for photodegradation. The RMS notes that the main soil metabolite, X11393729, which was also a major metabolite in both the hydrolysis study and the photolysis study with natural water, is also susceptible to aqueous photolysis and would not be expected to persist in an optically clear water body exposed to sunlight. Data in the phys/chem. properties section (Section B.2.1.10) indicates a molar extinction coefficient for X11393729 of $4301 \text{ L mol}^{-1} \text{ cm}^{-1}$ at neutral pH at 290 nm, suggesting, as for the parent, that the substance is susceptible to photolysis. Soil metabolite X11449757 also appears to be susceptible to photo-degradation with a molar extinction coefficient of $5535 \text{ L mol}^{-1} \text{ cm}^{-1}$ at neutral pH

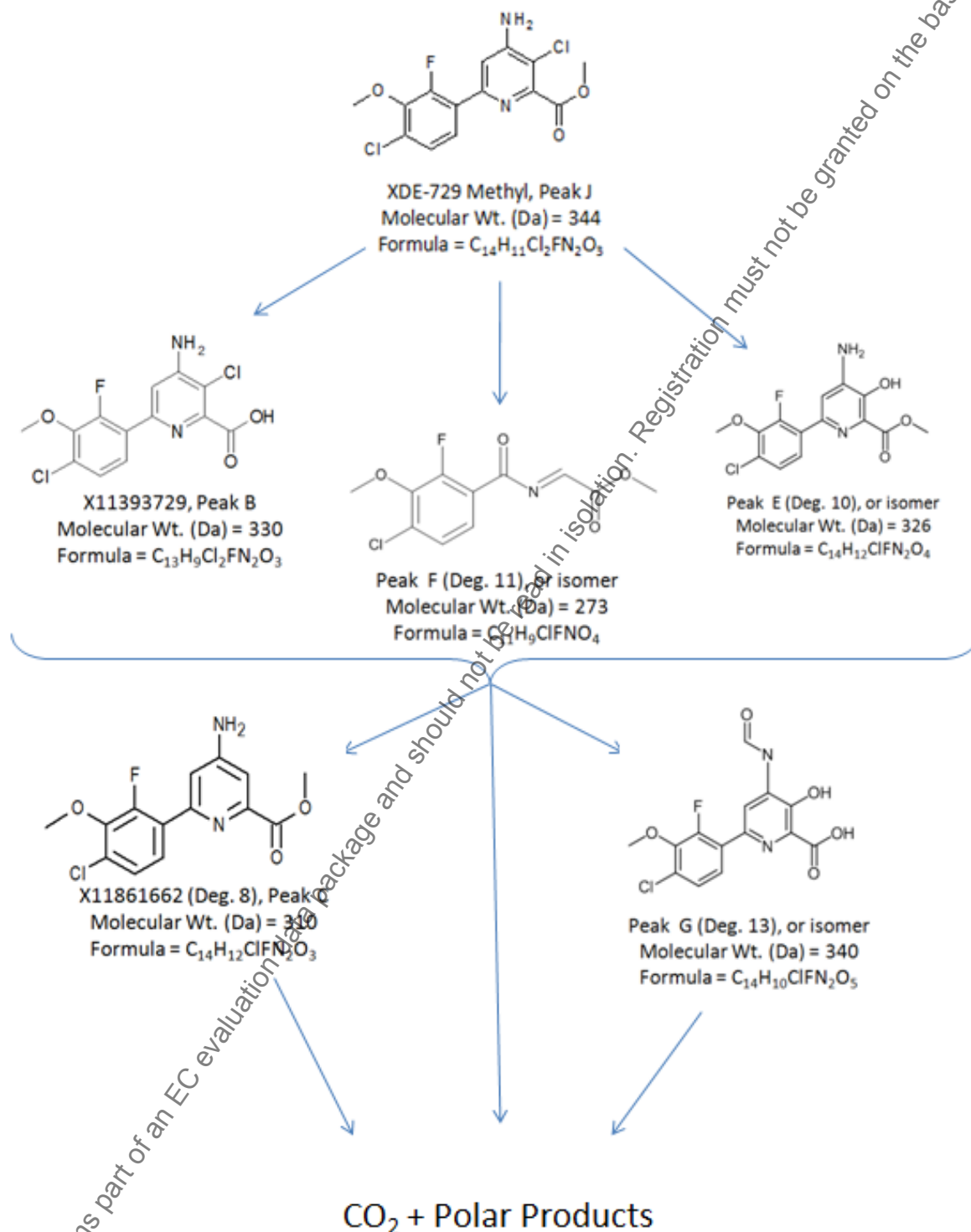
at 290 nm. However, the simulation of such rapid photo-degradation rate in FOCUS exposure modelling is not simple given that the water body is not differentiated by depth layers but by segment of horizontal distance. The Applicant has proposed a strategy for addressing aquatic risk as a result of rapid and extensive photolytic degradation in surface water, this being discussed in the section dealing with PEC_{sw} calculations (B.8.6.1). However, given that the a.s. and the two main soil metabolites appear to be very susceptible to aqueous photolysis, it is considered likely that these can be accommodated by the risk assessment by assessing the four identified aqueous photolysis metabolites.

The following degradation pathways were proposed for aqueous photolysis in pH 7 buffer and in natural water.

Proposed photolytic degradation pathway for XDE-729 methyl in pH 7 buffer



Proposed photolytic degradation pathway for XDE-729 methyl in natural water



A further non-guideline study to investigate aqueous photolysis under conditions of an Ecotox study on *Myriophyllum* sp indicated rapid degradation with DT50 less than 1 day (SFO kinetics) under unknown light conditions. By contrast, in dark conditions in the test medium at pH 7, 51 – 56% AR remained as unchanged XDE-729 methyl at study end (14 days). Scrutiny of chromatograms from illuminated samples suggested extensive degradation with multiple, mostly unidentified, peaks.

This is generally in agreement with the findings of the standard aqueous photolysis study which indicates that XDE-729 methyl degrades rapidly with formation of a large number of minor metabolites.

Ready biodegradability

A ready biodegradability study was conducted on the metabolite X11393729. Given the rapid degradation of XDE-729 methyl to X11393729 in the environment, this is considered acceptable. The study demonstrated that X11393729 would be classified as 'not readily biodegradable'. It is considered that this conclusion can be extrapolated to XDE-729 methyl.

Water/sediment study

A standard water/sediment study was conducted on XDE-729 methyl using two systems. The sediment properties ranged from weakly acid to weakly alkaline with a range of organic carbon content. The water/sediment systems are considered by the RMS to be appropriate. Measurements of redox potential suggest that the systems had aerobic water layers and anaerobic sediments. Mass balances recorded during the study were generally acceptable. However, it was noted that for day 0, the results were taken from water samples that specifically did not have any sediment associated with them at the time of dosing. The OECD 308 guideline suggests that both water and sediment should be analysed at all sample times. In terms of kinetic assessment, this does not pose an issue as any metabolite residues in the water at day 0 were added to the measured a.s. concentration. However, the main issue is whether this departure from the OECD guideline is sufficiently serious to invalidate the study. In the view of the RMS, whilst potentially important information on initial degradation and partitioning behaviour during the first minutes or hours after dosing in the complete system is absent, this is not a sufficiently serious departure to invalidate the study. Essentially, an absolute time zero sample should only contain parent and there should be no time for partitioning to sediment to occur, thus residues should only be present in the water layer at the immediate time of dosing the system.

XDE-729 methyl degraded rapidly in both systems with <10% AR remaining in the total system at 5 – 14 DAT. The more rapid degradation occurred in the Calwich Abbey Lake water/sediment system which had a higher microbial biomass, organic carbon and clay content and the higher pH. Dissipation from the water layer was also rapid with some partitioning into sediment. The highest amount of observed partitioning occurred in the Swiss Lake system, with up to 122% AR at 2 DAT. Interestingly, this was the system that theoretically would have had the lower adsorption potential of the two systems tested, but the higher level of observed partitioning may be related to the overall slower degradation of XDE-729 methyl in this system, e.g. the actual level of partitioning into sediment in the Calwich Abbey Lake system may be disguised by the rapid degradation. The highest observed partitioning into sediment in the Calwich Abbey Lake system was 7.3% AR at 2 DAT.

Extensive metabolite formation was also seen in both systems. Three metabolites were positively identified. Metabolite X11393729 was seen at 16.4 – 23.5% AR at 2 – 8 DAT in the total system but appeared to occur in greater amounts in the water phase, with 13.3 – 20.0% AR at 2 – 8 DAT in the water phase and 3.2 – 6.1% AR at 2 – 5 DAT in sediment. Decline was moderate in the Swiss Lake total system with a pronounced ‘tail’ 1.5 – 4% AR from 43 DAT to the study end. However, X11393729 was only sporadically detected at under 1% AR from 14 DAT in the Calwich Abbey Lake total system.

X11449757 was the principal metabolite with 75.6 – 76.7% AR at 8 – 22 DAT formed in total system. Similar concentrations were seen in water and sediment but peak concentrations appeared to occur earlier in water. This may indicate formation in both water and sediment and potential partitioning from water into sediment. Peak concentrations in the water phase were 44.4 – 48.3% AR at 5 – 22 DAT. In sediment, concentrations were 36.9 – 50.6% AR at 30 – 43 DAT. Dissipation from total system appeared to be relatively slow in the Calwich Abbey Lake system with 35 – 43% AR remaining at study end, but appeared to be more rapid in Swiss Lake system, with 16% remaining at study end.

A further metabolite, X11406790, was identified. This reached 23.4 – 23.6% AR in total system at 2-5 DAT, with maximum amounts observed in water and sediment at the same sample time. Maximum amounts in water were 12.8 - 16.5% AR at 2 - 5 DAT and in sediment were 7.0 – 10.6% at 2 – 5 DAT. Levels had declined to <5% AR by 8 – 22 DAT. X11406790 appeared to be formed at similar times to X11393729 and the proposed structure is the same as parent except for demethylation of the phenyl ring as opposed to demethylation of the pyridine ring as in X11393729. As such it is proposed as an additional precursor to formation of X11449757 which is formed by demethylation of both ring structures.

It is noted that these three metabolites were all identified as soil metabolites, but only X11393729 and X11449757 occurred at greater than 10% in soil. In addition, X11393729 was the principal metabolite in soil whereas X11449757 appears to be the principal metabolite in water/sediment systems. All three of these metabolites must be subject to an aquatic exposure assessment.

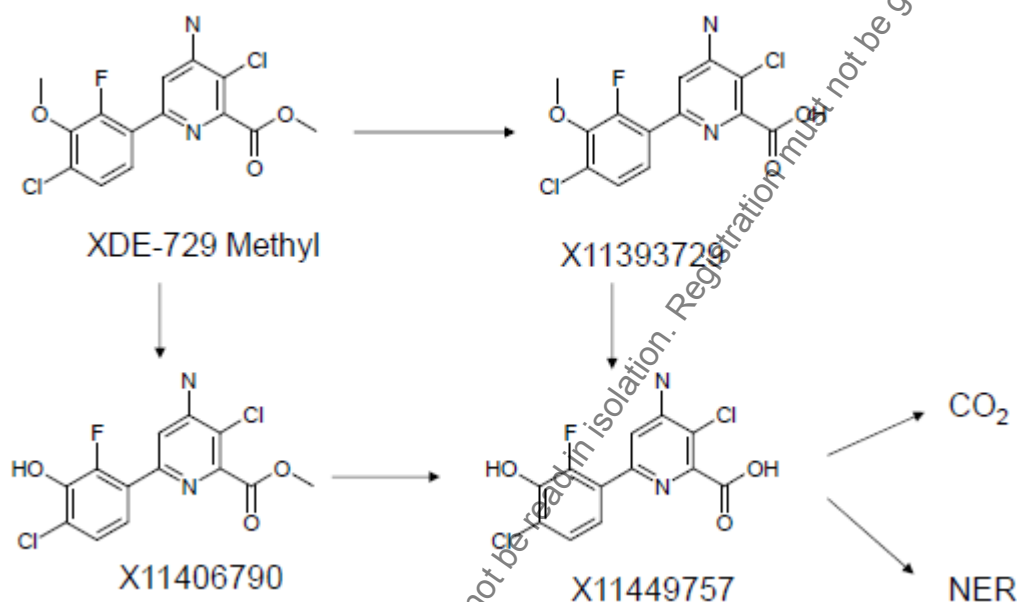
No other metabolites were identified. ‘Other’ radioactivity rose to a peak of 12.7% AR in the Swiss Lake system at study end, but this was the sum of numerous small chromatographic peaks, none of which accounted for >5% AR at any time.

Mineralisation was limited, particularly in the Calwich Abbey Lake system with <2% AR in the NaOH trap at study end (103 DAT). In the Swiss Lake system, there was 15.8% AR as CO² at study end with the phenyl labelled material, but only 5.1% AR with pyridine labelled material.

Similar levels of unextracted residues were observed in both systems at study end, with 42.5 – 45.4% AR with phenyl labelled material and 51.2 – 54.8% AR with pyridine labelled material.

The following degradation pathway was proposed for XDE-729 methyl in dark aerobic water/sediment systems.

Proposed metabolic pathway for XDE-729 methyl in dark aerobic water/sediment systems



The study authors only attempted calculations of degradation rates for parent and metabolites in the total system. These are shown below.

Summary of SFO DegT50 values (days) for XDE-729 methyl and metabolites in water/sediment total system

System	XDE-729 methyl	X11393729	X11406790	X11449757
Swiss Lake	4	11*	7*	38*
Calwich Abbey	0.8	2	1.5	87

*dissipation rate, calculated by top down approach

The Applicant considered that whilst there was relatively frequent sampling during the initial part of the water/sediment study, XDE-729 methyl had dissipated so quickly that the behaviour in the early part of the study needed to be investigated further. To this end, a 'supplementary' study was performed over 30 days with more frequent sampling particularly in the first week. Essentially the study was repeated with water/sediment systems sourced from the same locations as originally used. Phys/chem properties of the water/sediment systems were similar but not identical to those in the original study. Behaviour of XDE-729 methyl in the supplementary study was very similar. Metabolites X11393729, X11449757

and X11406790 were all observed and with similar behaviour. In the 'supplementary' study, X11393729 was formed at slightly lower levels in both systems, X11449757 was formed at higher levels in the Calwich Abbey system and X11406790 was formed at higher levels in the Swiss Lake system. Kinetic assessment of the new study for parent and metabolites showed very similar values. It is thus considered that it is acceptable to use the supplementary study as supportive information to the original water/sediment study and to use kinetic endpoints derived from the original study.

Standard FOCUS_{sw} modelling was performed for XDE-729 methyl and X11393729 at Steps 1-4. In addition, FOCUS_{sw} Steps 1-2 were performed for metabolites X11449757, X11406790 and aqueous photolysis metabolites Deg 10, Deg 11 and Deg 14. The results of the predicted surface water and sediment exposure have been used in ecotoxicological risk assessment. MS should note that these calculations assume a 70 day application interval for use on winter cereals. Consequently, MS should consider ensuring that a 70 day interval between applications is specified as a conditions of plant protection product authorisation.

FOCUS_{gw} modelling was performed for XDE-729 methyl, X11393729 and X11449757. The modelling indicated that none of the substances included in simulations were likely to exceed 0.1 µg/l on an annual average basis in shallow groundwater. MS should note that these calculations assume a 70 day application interval for use on winter cereals. Consequently, MS should consider ensuring that a 70 day interval between applications is specified as a conditions of plant protection product authorisation.

2.5.4 Fate and behaviour in air

XDE-729 methyl has a vapour pressure of 5.9×10^{-9} Pa at 20°C, water solubility of 1.66 – 1.69 mg/l at pH 5–9 and calculated Henry's Law constant of $1.20 - 1.23 \times 10^{-6}$ Pa m³/mol at pH 5–9. This would suggest that volatility of XDE-729 methyl from water or moist soil and leaf surfaces will be limited. The vapour pressure suggests that dry deposits will be unlikely to dissipate significantly via volatilisation.

The 'Atkinson' half life of 2.2 days suggests that there may be a possibility for long-range transport were XDE-729 methyl to enter the atmosphere. However, the low relative values of vapour pressure and Henry's Law constant suggest that volatilisation is unlikely from soil and leaf surfaces, and thus it is considered that the risk of long range transport of this active substance is very low. The RMS notes that recent EFSA conclusions have highlighted potential for long range transport of substances with an Atkinson half life >2 days as a result of aerosol formation during spraying operations. This possibility has not been addressed in this assessment. However, it is likely that any subsequent exposure of the environment as a result of long range transport will be well within that already considered by the existing environmental exposure and risk assessment.

An 'Atkinson' calculation was not presented for the main soil metabolite, X11393729, but vapour pressure (2×10^{-5} Pa at 20°C) and solubility data (0.1 – 46.1 g/l at pH 5 – 9) suggest that this metabolite is unlikely to volatilise.

2.6 Effects on non-target species

2.6.1 Effects on birds and mammals

At screening step, in a risk assessment conducted to the EFSA (2009) guidance, the acute and reproductive TERs for birds and mammals were above the trigger values for the representative use on winter and spring cereals.

Acute toxicity data for the representative formulation, GE-2573 was also submitted for birds and mammals. An acute risk assessment using these endpoints was carried out and the results were compared to the risk assessment with the active, XDE-729 Methyl. The TER's calculated were above the trigger values.

A low risk to birds and mammals via drinking water, secondary poisoning (from consumption of potentially contaminated fish and earthworms) and from biomagnification was also concluded.

It was considered that there were no relevant metabolites for XDE-729 Methyl that required further evaluation in the bird and mammal risk assessments. Any metabolites present in plants were also present in bird/mammal metabolism studies. These metabolites were all present at low levels (<10%) and were considered to be covered by the active risk assessment. Metabolites of XDE-729 Methyl have a very low potential for bioaccumulation and biomagnification with log K_{ow} values below the trigger value of 3. Therefore bioaccumulation of XDE-729 Methyl metabolites in soil organisms such as earthworms and aquatic organisms such as fish is negligible and not a major route of exposure to birds.

XDE-729 Methyl, XDE-729 Acid, X11406790 and X11449757 do not appear to exhibit endocrine-disrupting properties that would affect reproductive physiology or development of reproductive organs in wild mammals or birds. However, member states should note that there are currently no defined criteria for identifying endocrine disruptors under 2009/1107 and as such only a qualitative case can be made.

2.6.2 Effects on aquatic species

With the exception of aquatic plants, the acute and long-term toxicity/exposure ratios (TERs) for GF-2573, XDE-729 Methyl and the major metabolites are in excess of the Annex VI triggers for FOCUS Step 1 and/or Step 2.

XDE-729 Methyl and XDE-729 Acid are significantly more phytotoxic to the aquatic plant *Myriophyllum spicatum* than to *Lemna*; as a result the TER values for XDE-729 Methyl and XDE-729 Acid are below the Annex VI trigger for FOCUS Step 1, Step 2 and Step 3 for most application scenarios. The metabolites X11449757 and X11406790 showed low phytotoxicity towards *Myriophyllum* at the maximum concentration tested (100 µg/L) and as a result the TER values exceed the Annex VI triggers at FOCUS Step 1.

The risk from the formulated product was concluded as acceptable for all organism groups with the implementation of a 5m buffer zone to reduce spray drift (to address the risk to aquatic plants).

XDE-729 Methyl: Exposure of aquatic plants occurs principally via drift immediately following application of GF-2573. Consequently, for applications to winter cereals a 10 m buffer (for spring applications at 6.25 g/ha) or 20 m buffer (for autumn applications at 7.82 g/ha) will provide adequate mitigation for all FOCUS surface water scenarios. For applications, at 6.25 g/ha, to spring sown cereals a 10 m buffer will provide adequate mitigation. All buffers implemented must reduce exposure via spray drift and runoff.

XDE-729 Acid: Exposure of aquatic plants is predicted to occur principally via drainflow and run-off. Consequently, **for autumn applications at 7.82 g/ha to winter cereals acceptable risk from the acid to *Myriophyllum* could not be demonstrated for FOCUS scenarios D1 ditch and stream, D2 ditch and stream and D6 ditch. Spring applications to winter sown cereals at a rate of 6.25 g/ha result in unacceptable risk to *Myriophyllum* for scenarios D1 ditch, D2 ditch and stream, and D6 ditch.** Application in spring to spring sown cereals at 6.25 g/ha results in acceptably low risk to *Myriophyllum* from the acid for all FOCUS scenarios.

As an overall acceptable risk from the acid cannot be demonstrated using FOCUS modelling and risk mitigation, member states should consider carefully which scenarios are relevant in their national assessments. Likewise appropriate mitigation should be considered at member state level in line with individual national requirements.

The risk to the most sensitive organism tested (*Myriophyllum spicatum*) was also assessed using growth rate endpoints from the lab data, in line with the draft EFSA aquatic guidance document (EFSA Journal 2013;11(7):3290). The outcome is not greatly different, with only the exact level of mitigation required for each proposed use and unresolved FOCUS scenarios differing. Again member states may wish to consider this approach when conducting their national assessments.

The active substance was concluded as having low bioaccumulation potential in fish (BCF < 1000, 95% depuration time of 1.6 days).

2.6.3 Effects on bees

An acceptable risk was demonstrated at first tier for the active substance, XDE-729 Methyl and the representative formulation, GF-2573. The contact and oral hazard quotients derived using the toxicity endpoints from laboratory acute toxicity tests are below the Annex VI trigger value. It can therefore be concluded that if used according to the proposed GAP, XDE-729 methyl and the formulation GF-2573 demonstrate an acceptable risk to bees.

2.6.4 Effects on other arthropod species

An acceptable in-field and off-field risk to non-target arthropods from the proposed use of GF-2573 was demonstrated at first tier. Based on an ESCORT 2 first tier risk assessment the off-field and in-field hazard quotients were below the Annex VI trigger value. Therefore use of the representative formulation in accordance with the proposed GAP does not pose a significant risk to non-target arthropod species in both in-field and off-field habitats.

2.6.5 Effects on earthworms

An acceptable acute and chronic risk to earthworms has been demonstrated for the representative formulation GF-2573, the active XDE-729 Methyl, the major metabolites XDE-729 Acid (X11393729) and X11449757 and all non-extractable residues. All TER values calculated were above the acute and chronic Annex VI trigger values.

2.6.6 Effects on other soil non-target macro-organisms

An acceptable chronic risk to non target soil macro-organisms has been demonstrated for XDE-729 Methyl and the major metabolites XDE-729 Acid (X11393729) and X11449757. All TER values calculated were above the chronic Annex VI trigger values.

For soil micro-organisms, the concentrations for which <25% effects were observed, were all in excess of the PEC_{soil} values. Therefore it can be concluded that the risk to soil micro-organisms is acceptable for the use of GF-2573 on cereals if applied according to the proposed GAP.

2.6.7 Effects on other non-target organisms (flora and fauna) believed to be at risk

For the formulation GF-2573 the TER's for vegetative vigour and seedling emergence exceeded the Annex VI trigger value, with a 5m buffer zone. Therefore, an acceptable risk has been demonstrated from exposure to the

representative formulation, GF-2573 providing a 5 m buffer zone or equivalent risk mitigation is implemented.

For the metabolite XDE-729 Acid the TER for seedling emergence exceeds the proposed Annex VI trigger value, with a 5m buffer zone. Therefore, an acceptable risk has been demonstrated from exposure to XDE-729 acid, providing a 5 m buffer zone or equivalent risk mitigation is implemented. The result from this risk assessment demonstrates that XDE-729 Acid poses no additional risk then that already demonstrated from exposure to GF-2573 and as such the active XDE-729 Methyl, which also results in a 5m buffer zone or equivalent risk mitigation.

For the soil metabolite, X11449757 the TER for seedling emergence exceeds the proposed Annex VI trigger value at first tier and as such, no additional buffer zone or risk mitigation is required.

Overall, acceptable risks for non target plants has been demonstrated following exposure to the representative formulation, GF-2573 assuming **a 5m buffer zone or equivalent risk mitigation is implemented.**

2.6.8 Effects on biological methods of sewage treatment

The proposed EC_{50} for XDE-729 methyl is > 981 mg a.s./L. When compared to the worst-case FOCUS step 1 PEC_{sw} for all proposed applications (1.197 $\mu\text{g/L}$), it can be concluded that an acceptable risk from XDE-729 methyl has been demonstrated for microbial activity in these systems.

LEVEL 3**XDE-729 Methyl
(Halauxifen-methyl)**

**LEVEL 3: CONCLUSIONS AND PROPOSED DECISION WITH RESPECT TO THE
CRITERIA AND REQUIREMENTS OF REGULATION (EC) NO. 1107/2009**

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

3 PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1 Background to the proposed decision

3.1.1 Proposal on acceptability against the decision-making criteria – Article 4 and Annex II of Regulation (EC) No. 1107/2009

3.1.1.1 Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	X		It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with for XDE-729 Methyl, with the representative product formulated as an EC for use as a spray on spring and winter cereals. Refer to Section 1.5.3.1, Level 1 for details of uses considered.
3.1.1.2 Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		It is considered that a sufficiently complete dossier has been submitted to establish that risks are acceptable and no critical uses are identified, issues that are considered to not be finalised (see 3.1.5 below) may reasonably be expected to be addressed by Member States when considering product authorisations.
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.	N/A	N/A	See i) above.

3.1.1.3 Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.	X		(a) the minimum degree of purity of the active substance; 930 g/kg (based on pilot scale material) (b) the nature and maximum content of certain impurities; N/A (c) restrictions arising from the evaluation of the information referred to in Article 8 of 1107/2009 taking account of the agricultural, plant health and environmental, including climatic, conditions in question; N/A (d) type of preparation; N/A (e) manner and conditions of application; N/A (f) submission of further confirmatory information to Member States, the Commission and the European Food Safety Authority, (the Authority), where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge; N/A (g) designation of categories of users, such as professional and non-professional; N/A (h) designation of areas where the use of plant protection products, including soil treatment products, containing the active substance may not be authorised or where the use may be authorised under specific conditions; N/A

				(i) the need to impose risk mitigation measures and monitoring after use; <u>Mitigation Required:</u> • Member States should consider the risk to aquatic plants • Member States should consider the risk to Terrestrial non-target plants (j) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009. <i>Explain if some of the information to be submitted relates only to specified products/uses/use scenarios]</i> N/A
3.1.1.5 Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		The data submitted are sufficient to establish an Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier:	X		a) Sufficient data were provided in the dossier to propose a residue definition in plants and animals of XDE-729 methyl and XDE-729 acid for risk assessment and monitoring purposes (plant metabolism studies were conducted on wheat and turnip, animal metabolism studies were conducted on poultry and lactating goats). Residue definitions in rotational crops were not required for the notified uses. b) Sufficient residues data according to the GAP were provided

	(b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			for the representative use on cereals in the northern and southern EU. This data was supported by appropriate storage stability data and methods of analysis. Based on results from the confined rotational crop study, no field residue trials with succeeding crops are expected to be necessary. c) Sufficient data were presented in the dossier to demonstrate that residues of XDE-729 methyl are not expected to concentrate in processed fractions of grain. d) Sufficient data were available to propose an MRL for XDE-729 methyl for the following cereal grains: barley (including spring and winter barley) and by extrapolation wheat, to include spring wheat, winter wheat, soft wheat, durum wheat, triticale and spelt), and rye of 0.02 mg/kg. Appropriate monitoring methods are available to enforce this MRL. MRLs for commodities of animal origin or other crops were not required for the notified uses. e) Not relevant.
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	X		
Efficacy				
	Yes	No		
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		For approval of an active substance 'a plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements: a) it shall be sufficiently effective and c) it shall not have any unacceptable effects on plants or plant products'. The applicant has addressed this requirement.

Relevance of metabolites			
		Yes	No
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X	
[Explain if this applies to all or some of the representative uses/use scenarios/products]			
Composition			
		Yes	No
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereoisomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X	
XDE-729 methyl is manufactured with a minimum purity of 93.0% (930 g/kg) g/kg. None of the impurities are considered to be of toxicological, ecotoxicological or environmental concern. Acceptable data have been submitted for pilot scale manufacture of XDE-729 methyl technical material and a provisional specification may be proposed. Following scale-up from pilot plant to full scale manufacture new 5-batch analysis supporting the commercial scale technical specification must be submitted. In addition the toxicological significance of any changes in the impurity profile must be addressed. In the case of XDE-729 Methyl, the RMS was unable to conclude that material of the proposed technical specification is toxicologically or ecotoxicologically equivalent to the material used in the XDE-729 Methyl toxicity/ecotoxicity studies. The RMS proposes that the equivalence of the technical specification to the material used in the toxicity/ecotoxicity testing is addressed when the final technical specification of XDE-729 Methyl has been determined, because it is possible that the quantity of an impurity present in the 5-batch analysis, but not in the batches used for the toxicological/ecotoxicological studies, may be lower in the final specification, such that equivalence is no longer an issue. See Volume 4 for further details regarding the specific			

				concerns and data requirements for future submission of batch analysis for full scale manufacture.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	N/A		Not applicable. There is no FAO specification for XDE-729 Methyl.
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted	N/A		Not applicable. There is no FAO specification for XDE-729 Methyl.
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	X		Acceptable methods of analysis have been provided for the quantification of the active substance XDE-729 methyl technical material. These methods were acceptably validated in accordance with SANCO/3030/99 rev. 4. Refer also to Level 2.2.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		Acceptable methods of analysis have been provided for the quantification of residues of XDE-729 methyl and XDE-729 acid in plants and animal commodities and XDE-729 methyl and XDE-729 acid and relevant metabolites in environmental matrices. These methods were validated in accordance with SANCO/825/00 rev. 8.1. The LOQs are appropriate for the enforcement of MRLs and Directive 2000/60/EC. Refer also to Level 2.2.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		Refer to Level 2.2 for further details

Impact on human health			
Impact on human health - ADI, AOEL, ARfD			
		Yes	No
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	X	
			The ADI of 0.058 mg/kg/day is proposed based on the application of a standard assessment factor of 100 to the NOAEL of 5.78 mg/kg/day, identified in a rabbit developmental toxicity study. The ARfD of 2.5 mg/kg is proposed based on the application of an assessment factor of 100 to the NOAEL of 250 mg/kg identified in an acute oral neurotoxicity study in rats. The AOEL of 0.058 mg/kg/day is proposed based on the application of a standard assessment factor of 100 to the NOAEL of 5.78 mg/kg/day, identified in a rabbit developmental toxicity study. Refer also to section 2.3, level 2.
Impact on human health – proposed genotoxicity classification			
		Yes	No
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, the substance SHOULD BE classified or proposed for classification , in accordance with the provisions of Regulation (EC) No 1272/2008, as mutagen category 1A or 1B.		X
			XDE-729 Methyl and its major metabolite XDE-729 Acid tested negative in <i>in vitro</i> assays for gene mutation and clastogenicity, and XDE-729 Acid tested negative in an <i>in vivo</i> micronucleus test.
Impact on human health – proposed carcinogenicity classification			
		Yes	No
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by		X
			A standard carcinogenicity study in the rat and one in the mouse demonstrate that the major metabolite XDE-729 Acid is not carcinogenic. This conclusion is also applicable to XDE-729 Methyl at oral exposure levels of up to 10 mg/kg/day.

	the Authority, the substance SHOULD BE classified or proposed for classification , in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B .			
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.	N/A	N/A	Not applicable
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, the substance SHOULD BE classified or proposed for classification , in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B .		X	The reproductive toxicity of XDE-729 Methyl and/or its major metabolite XDE-729 Acid has been adequately investigated in a rat two-generation study and in rat and rabbit developmental toxicity studies. These studies clearly demonstrated that XDE-729 Methyl does not possess specific hazardous properties in relation to fertility, reproductive performance or development.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and	N/A	N/A	Not applicable

	where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that the substance SHOULD BE classified or proposed for classification in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties		X	As indicated above, no evidence of carcinogenicity or reproductive toxicity hazard was seen in the standard carcinogenicity and reproductive toxicity tests
ii)	It is considered that the substance SHOULD BE classified or proposed for classification in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and in addition the RMS considers the substance has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties		X	No evidence of a reproductive toxicity hazard was seen in the reproductive toxicity tests and no evidence of adverse effects on endocrine organs was seen in the standard short-term and long-term repeated dose toxicity studies.
iii)	Linked to either i) or ii) immediately above. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.	N/A	N/A	Not applicable

Fate and behaviour in the environment			
Persistent organic pollutant (POP)			
	Yes	No	
It is considered that the active substance FULFILS the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	XDE-729 methyl does not fulfil the POP criteria laid out in Regulation 1107/2009. The DT50 in water, soil and sediment are shorter than the criteria for persistence. The bioconcentration factor in fish is 217 (< 5000) and the log K _{ow} is < 6 (3.76). Although the atmospheric DT50 is >2 days (2.2 days), volatilisation is expected to be low and long-range transport unlikely.
Persistent, bioaccumulative and toxic substance (PBT)			
	Yes	No	
It is considered that the active substance FULFILS the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		X	XDE-729 methyl fulfils 0/3 of the PBT criteria laid out in Regulation 1107/2009. The DT50 in water, soil and sediment are shorter than the criteria for persistence. The bioconcentration factor in fish is 217 (< 2000), and the lowest NOEC for aquatic organisms is >0.01 mg a.s./L (0.0115 mg/L for <i>Cyprinodon variegatus</i>). The substance is not classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) and there is no other evidence of chronic toxicity as identified by the classifications STOT RE 1 or STOT RE 2.
Very persistent and very bioaccumulative substance (vPvB).			
	Yes	No	
It is considered that the active substance FULFILS the criteria of a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	XDE-729 methyl does not fulfil the vPvB criteria laid out in Regulation 1107/2009. The DT50 in water, soil and sediment are shorter than the criteria for persistence. The bioconcentration factor in fish is 217 (< 5000)

Ecotoxicology				
		Yes	No	
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.	X		Refer to level 2, section 2.6.
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance HAS endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	Based on evidence, XDE-729 Methyl, XDE-729 Acid, X11406790 and X11449757 do not appear to exhibit endocrine-disrupting properties that would affect reproductive physiology or development of reproductive organs in wild mammals or birds. However, Member States should note that there are currently no defined criteria for identifying endocrine disruptors under 2009/1107 and as such only a qualitative case can be made.
	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.	N/A	N/A	Not applicable. See above point, no endocrine disrupting properties.
	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products	X		An acceptable risk to honey bees was demonstrated at tier 1. See level 2, section 2.6.3.

	containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.			
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		Based on the metabolism data submitted for wheat and turnip, residues should be defined as follows: Crops (MRL and monitoring): XDE-729 methyl and XDE-729 acid Crops (Risk Assessment): XDE-729 methyl and XDE-729 acid Based on the metabolism data submitted for goats and hens, residues should be defined as follows: Animal products (MRL and monitoring): XDE-729 methyl and XDE-729 acid Animal products (Risk Assessment): XDE-729 methyl and XDE-729 acid Residue definition in rotational crops: Not required.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction	X		XDE-729 methyl and its two main soil metabolites X11393729 and X11449757 were not predicted to exceed 0.1 µg/l annual average at 1m depth in any of the FOCUS Groundwater scenarios.

	products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.			
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3.1.2 Proposal – Candidate for substitution

Candidate for substitution			
		Yes	No
	It is considered that the active substance shall be approved as a candidate for substitution		X
			XDE-729 methyl does not meet the criteria to be considered as a candidate for substitution (as below): <i>its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories,</i> <i>— it meets two of the criteria to be considered as a PBT substance (currently 0 from fate and ecotox areas)</i> <i>— there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones),</i> <i>— it contains a significant proportion of non-active isomers,</i> <i>— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3,</i>

			— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4, — if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5.]
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3.1.3 Proposal – Low risk active substance

Low-risk active substances			
	Yes	No	
It is considered that the active substance shall be considered of low risk. In particular it is considered that the substance should NOT be classified or proposed for classification in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that the substance is NOT: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100,		NO	The longest soil half-life for XDE-729 methyl is 43 days (UK, Spring) based on a field study. This is below the 60 d trigger for substances to be considered 'low risk'. The active substance is not classified as carcinogenic, mutagenic, toxic to reproduction, sensitising, very toxic or toxic, or corrosive. It also does not demonstrate neurotoxic or immunotoxic effects and does not appear to exhibit endocrine-disrupting properties (however, it should note that there are currently no defined criteria for identifying endocrine disruptors). However, XDE-729 methyl is toxic to aquatic organisms [proposal for classification with H400/410: Very toxic to aquatic life with long lasting effects (acute/chronic category 1)]. This is based on the following effects: i) <i>Myriohyllum spicatum</i> 14 d E_rC₅₀ 0.000393 mg a.s./L ii) <i>Myriohyllum spicatum</i> 14 d NOEC <0.0000617 mg a.s./L iii) substance not 'rapidly biodegradable' Therefore, XDE-729 methyl can not be considered a low risk substance in accordance with Regulation (EC) No. 1107/2009.

	— is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.			
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3.1.4 List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
None				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Determination of surface tension of the pure active substance.				Final report available (not submitted to RMS)
Storage Stability and Package Corrosion Characteristics of GF-2573 in PET and F-HDPE; Two year Ambient Study ongoing (FOR-10-40.01).				Final report available (not submitted to RMS)
3.1.4.3 Data on uses and efficacy				
None				

3.1.4.4 Data on handling, storage, transport, packaging and labelling				
None				
3.1.4.5 Methods of analysis				
A revision of the 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 Mass Spectrometry Detection, Dow AgroSciences LLC Study Number 110004. The report will be revised to include the confirmatory transition data, including calibration, recovery and precision. Please note, in the absence of this revision, the method has still been deemed fit for purpose.				Final report available (not submitted to RMS)
3.1.4.6 Toxicology and metabolism				
None				
3.1.4.7 Residue data				

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XDE 729 Methyl (Halauxifen-methyl)

Volume 1, Level 3

X11393728 (XDE 729 Methyl) and X11393729 (XDE 729): Residue Stability Study in Crops under Frozen Storage Conditions, 24 month study ongoing.				Final report available (not submitted to RMS)
Frozen Storage Stability of Residues of XDE 729 Methyl Ester, XDE 729 Acid, and X11449757 in Animal Matrices –24 month storage stability study ongoing.			Final report available Feb. 2014	
Storage Stability of Residues of XDE 729 Methyl Ester, XDE 729 Acid, and the Metabolite X11449757 in Soil, 24 month study ongoing.			Final report available May 2014	
3.1.4.8 Environmental fate and behaviour				
None				
3.1.4.9 Ecotoxicology				
None				

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3.1.5 Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	Relevance in relation to representative use(s)
None	-

3.1.6 Critical areas of concern

An issue is listed as a critical area of concern:

- (a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
- (b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	Relevance in relation to representative use(s)
Atmospheric (Atkinson) half-life = 2.2 days.	Substance applied in the field by hydraulic sprayers, possibility of aerosol formation. [See Level 2, Section 2.5.4 for further RMS comment]

3.1.7 Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)

All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		Use "A" (X ¹)	Use "B" (X ¹)
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified		
	Assessment not finalised		
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L ^(a) breached		
	Assessment not finalised		
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.

(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	Justification
Toxicology	Subject to Member State views during the commenting period of the peer review it may be necessary to discuss the mode of action (MoA) for XDE-729 Methyl induced liver effects in rodents.
Environmental Fate and Behaviour	Possibility of pH dependence of degradation of X11393729 and X11449757. The need to perform environmental exposure modelling using soil adsorption K_f for XDE-729 methyl, X11393729 and X11449757.

3.1.9 Critical issues on which the Co-RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	Opinion of Co-RMS	Opinion of RMS
Mode of action (MoA) for XDE-729 Methyl induced liver effects in rodents.	The co-RMS (France) is of opinion that the MoA for XDE-729 Methyl induced liver effects is not clearly demonstrated. This is because the partial AhR agonism cannot alone explain the strong CYP 1A1 gene expression increase observed in rat after XDE-729 Methyl exposure. Other MoAs could be involved such as stabilisation of CYP1A1 mRNA, activation of AhR via other signalling pathways (see Vol 3, Section B.6.5.3). Nevertheless, although there is disagreement regarding the MoA for rodent liver effects, the co-RMS agrees that the bridging strategy based on the demonstration of the saturation of hydrolysis of XDE-729 Methyl may be acceptable and that the ADI, ARfD and AOEL proposals by the RMS are appropriate.	The Applicant proposes that XDE-729 Methyl induces liver effects in rodents via an AhR-mediated MoA. The RMS agrees with the Applicant.

3.2 PROPOSED DECISION

It is proposed that:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

3.3 RATIONALE FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE**3.3.1 Particular conditions proposed to be taken into account to manage the risks identified**

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
Risk to aquatic plants	Applies to all representative uses on cereals
Risk to terrestrial non-target plants	Applies to all representative uses on cereals

Appendix I

APPENDIX I: STANDARD TERMS AND ABBREVIATIONS

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

Technical Terms

A	ampere
Ach	acetylcholine
Ache	acetylcholinesterase
ADI	Acceptable Daily Intake
ADP	adenosine diphosphate
AE	acid equivalent
AFID	alkali flame-ionization detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD50	approximate median lethal dose 50%
ALT	alanine aminotransferase (SGPT)
AOEL	Acceptable Operator Exposure Level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathie
BSP	bromosulfophthalein
Bt	bacillus thuringiensis
Bti	bacillus thuringiensis israelensis
Btk	bacillus thuringiensis kurstaki
Btt	bacillus thuringiensis tenebrionis
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10 ⁻²)
°C	degree celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase

CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of variation
Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days post inoculation
DRES	dietary risk evaluation system
DT	disappearance time
DT ₅₀	period required for 50 percent dissipation (define method of estimation)
DT ₉₀	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ϵ	decadic molar extinction coefficient
EC ₅₀	effective concentration
ECD	electron capture detector
ECU	European currency unit
ED ₅₀	median effective dose
EDI	estimated daily intake
ELISA	enzyme lined immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F ₀	parental generation
F ₁	filial generation, first
F ₂	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionization detector
FOB	functional observation battery
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	Good Agricultural Practice

GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulosevirus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionization detector
HPAEC	high performance anion exchange chromatography
HPLC	high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H _s	Shannon-Weaver index
Ht	haematocrit
I	indoor
I ₅₀	inhibitory dose, 50%
IC ₅₀	median immobilisation concentration
ICM	integrated crop management
ID	ionization detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal

IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	<i>in vitro</i> fertilization
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H) ¹³
K _{ads}	adsorption constant
K _{des}	apparent desorption coefficient
K _{oc}	organic carbon adsorption coefficient
K _{om}	organic matter adsorption coefficient
kg	kilogram
L	litre
LAN	local area network
LASER	light amplification by stimulated
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography - mass spectrometry
LC ₅₀	lethal concentration, median
LD ₅₀	lethal dose, median; dose letalis media
LCA	life cycle analysis
LC _{Lo}	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD ₅₀	lethal dose, median; dosis letalis media
LD _{Lo}	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of determination
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometer (micron)
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram

mg	milligram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mol	Mol
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
mM	Milimoles
MRL	maximum residue level
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NAEL	no adverse effect level
nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nonometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OM	organic matter
op	organophosphorous pesticide
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)

PEC	Predicted Environmental Concentration
PEC _A	predicted environmental concentration in air
PEC _S	predicted environmental concentration in soil
PEC _{SW}	predicted environmental concentration in surface water
PEC _{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the dissociation constant)
PNEC	predicted no effect concentration
po	by mouth
P _{ow}	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PPP	plant protection product
ppq	parts per quadrillion (10 ⁻²⁴)
ppt	parts per trillion (10 ⁻¹²)
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r ²	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
Rf	retardation factor
RfD	reference dose
RH	relative humidity
RL ₅₀	median residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	rotations per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography

sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STM	supervised trials median residue
t	tonne (metric ton)
$t_{1/2}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TC_{Lo}	toxic concentration, low
TID	thermionic detector, alkali flame detector
TD_{Lo}	toxic dose low
TDR	time domain reflectrometry
TER	Toxicity Exposure Ratio
TER_1	toxicity exposure ration for initial exposure
TER_{ST}	toxicity exposure ration following repeated exposure
TER_{LT}	toxicity exposure ration following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic carbon
Temcard	Transport emergency card
trNA	transfer ribonucleic acid
TSH	Thyroid stimulating hormone (thyrotropin)

TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Organisations and Publications

ACPA	American Crop Protection Association
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVD	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Limited
COREPER	Comite des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETO	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EHC (number)	Environmental Health Criteria (number)

EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organisation
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organisation of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organisation
IMO	International Maritime Organisation
IOBC	International Organisation for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organisation
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation

NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Centre for Toxicological Research (USA)
NGO	non-governmental organisation
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Système International d'Unités
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organisation
WTO	World Trade Organisation
WWF	World Wildlife Fund

Appendix II

APPENDIX II: SPECIFIC TERMS AND ABBREVIATIONS

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

Technical Terms

ADME	adsorption, distribution, metabolism and excretion
ADR	European agreement concerning the international carriage of dangerous goods by road
AR	applied radioactivity
AUC	area under curve
CHO	Chinese hamster ovary
EC	emulsifiable concentrate
EVOH	ethyl vinyl alcohol
HDPE	high density polyethylene
HPT	hypothalamus-pituitary-testicular
K _{ads}	adsorption constant
K _F	freudlich coefficient
K _{OH}	hydroxyl radical rate constant
K _{OW}	octanol water partition coefficient
LH	Luteinizing Hormone
LOQ	limit of quantification
MATC	Maximum Acceptable Toxic Concentration
MMAD	mass median aerodynamic diameter
Mbq	Mega becquerels
MS	Member State
MWHC	maximum water holding capacity
NMS	Northern Member State
OM	Organic Matter
P ₀ / P ₁	parental generation, first (author dependent)
PCN	potato cyst nematode
PDE	potential dermal exposure
PEC _a	predicted environmental exposure in air
PEC _{gw}	predicted environmental exposure in ground water
PEC _s	predicted environmental exposure in soil
PEC _{sw}	predicted environmental exposure in surface water
PELMO	Pesticide Leaching Model
PHED	Pesticide Handlers Exposure Database
pKa	dissociation constant
POEM	Predictive Operator Exposure Model
PPE	personal protective equipment
r ²	correlation coefficient
RPE	respiratory protective equipment
RSD	relative standard deviation
s	second
SC	suspension concentrate
SMS	Southern Member State
TER	toxicity exposure ratio
TLC	thin layer chromatography
WP	wettable powder

Organisations and Publications

BBA	Federal Biological Research Centre for Agriculture and Forestry (Germany)
EPA	Environmental Protection Agency (USA)
Defra	Department for the Environment Food and Rural Affairs (UK)
CRD	Chemicals Regulation Directorate (UK)

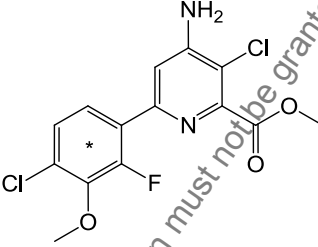
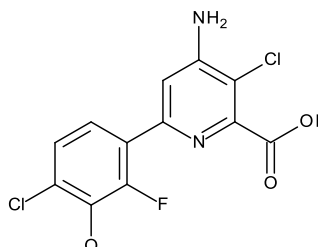
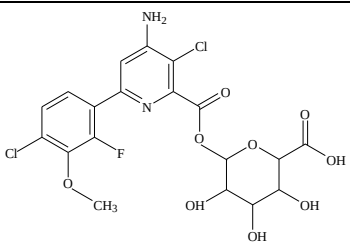
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Appendix III

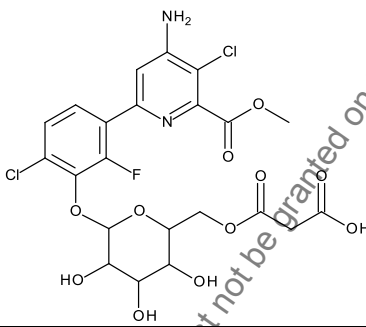
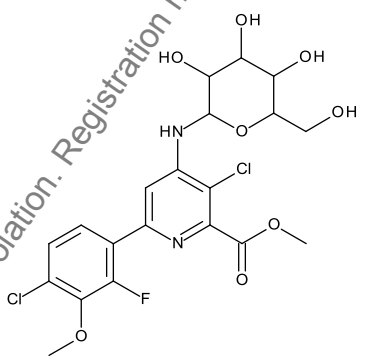
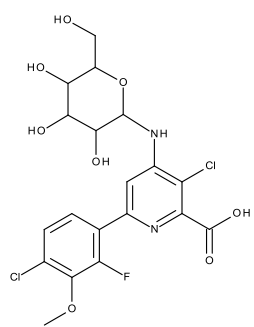
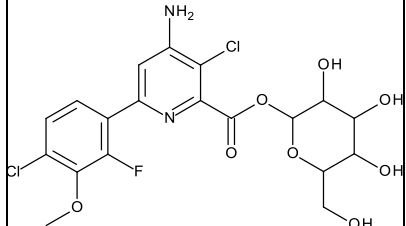
APPENDIX III: LIST OF METABOLITES IN THE ENVIRONMENT, PLANTS AND ANIMALS

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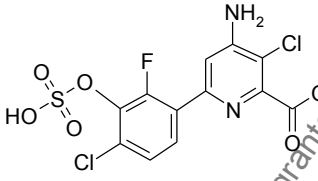
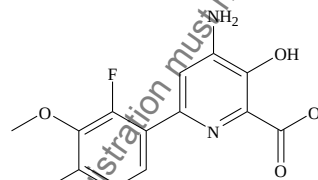
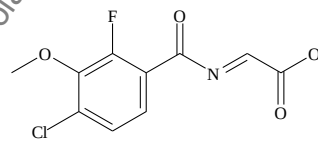
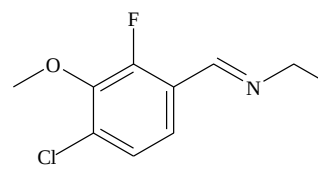
List of metabolites in the environment, plants and animals

Abbreviation	Synonyms	DAS code	Chemical Name	Structure	Occurrence/comments
XDE-729 methyl	XDE-729 ME XDE-729 ME PAI XDE-729 Methyl Ester XDE-728 XR-729	X11393728	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate (former IUPAC name for XDE-729 methyl) 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-pyridine-2-carboxylic acid methyl ester		Active Substance
XDE-729 acid	XDE-729 TGAI XDE-729 XR-729	X11393729	4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (former IUPAC name for XDE-729 acid) 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-pyridine-2-carboxylic acid		Acid of active substance
Acyl-glucuronide conjugate of X11393729	None	None	-		Formed during rat metabolism

Abbreviation	Synonyms	DAS code	Chemical Name	Structure	Occurrence/comments
None	None	X11406790	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)pyridine-2-carboxylate		Formed during plant metabolism (cereal and root crop) and animal metabolism (ruminant and poultry). Water Sediment
None	None	X11861662	methyl 4-amino-6-(4-chloro-2-fluoro-3-hydroxyphenyl)pyridine-2-carboxylate		Formed through dechlorination of XDE-729. X11861662 is an aqueous photodegradation product; it is proposed that it is formed by photolysis of XDE-729 methyl upon the leaf surface.
None	None	X11449757	4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid		Formed during plant metabolism (root and cereal crops) and animal metabolism (ruminant, poultry and rat). Soil Water Sediment
X11406790 glucose conjugate	None	See Abbreviation	-		Formed during plant metabolism (observed in cereal crops, proposed but not observed in root crops).

Abbreviation	Synonyms	DAS code	Chemical Name	Structure	Occurrence/comments
X11406790 malonyl-glucose conjugate	None	X12245409	-		Formed during plant metabolism (cereal and root crops).
XDE-729 Methyl glucose conjugate (2 anomers)	None	None	-		Formed during plant metabolism (root crops).
X11393729 glucose conjugate	None	See Abbreviation	-	 or 	Formed during plant metabolism (root crops).

Abbreviation	Synonyms	DAS code	Chemical Name	Structure	Occurrence/comments
Sulphate conjugate of X11449757	None	See Abbreviation	4-amino-3-chloro-6-(4-chloro-2-fluoro-3-sulfooxy-phenyl)pyridine-2-carboxylic acid		Found in the ruminant, poultry and rat metabolism studies.
Glucuronide conjugate of X11449757	None	See Abbreviation	-		Formed during rat metabolism
N- or O-glucuronic acid conjugate of X11406790	None	See Abbreviation	6-[[3-chloro-6-(4-chloro-2-fluoro-3-hydroxy-phenyl)-2-methoxycarbonyl-4-pyridyl]amino]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid or 6-[3-(4-amino-5-chloro-6-methoxycarbonyl-2-pyridyl)-6-chloro-2-fluorophenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid	 or isomer	Found in the ruminant and rat metabolism studies.
N-glucuronic acid conjugate of XDE-729 methyl	None	See Abbreviation	6-[[3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-2-methoxycarbonyl-4-pyridyl]amino]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid	 or isomer	Found in the ruminant metabolism study.

Abbreviation	Synonyms	DAS code	Chemical Name	Structure	Occurrence/comments
Sulphate conjugate of X11406790	None	See Abbreviation	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-sulfooxyphenyl)pyridine-2-carboxylate	 or isomer	Found in the ruminant and poultry metabolism studies.
Deg 10			methyl 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-3-hydroxypyridine-2-carboxylate	 or isomer	Aqueous photolysis
Deg 11			methyl (2E)-3-aza-4-(4-chloro-2-fluoro-3-methoxyphenyl)-4-oxobut-2-enoate	 or isomer	Aqueous photolysis
Deg 14			(3E)-3-aza-4-(4-chloro-2-fluoro-3-methoxyphenyl)but-3-enal	 or isomer	Aqueous photolysis

Appendix IV

APPENDIX IV: GUIDANCE DOCUMENTS USED IN THIS ASSESSMENT

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

GUIDANCE DOCUMENTS USED IN THIS ASSESSMENT

General

- Guideline developed within the Standing Committee on Plant Health with regard to the applicability of Good Laboratory Practice to data requirements according to Annexes II, Part A and III part A of Council Directive 91/414/EEC (7109/VI/94 Rev. 6 14/07/95).

Volume 3 Annex B2: Physicochemical properties

- WHO/FAO. 2002. Pesticide Specifications. Manual on development and use of FAO and WHO specifications for pesticides. Series FAO Plant Production and Protection Papers, Rome, 2002
- WHO/FAO. 2010. Manual on development and use of FAO and WHO specifications for pesticides. Second revision of the first edition. Rome, 2010
- EU Guidance Document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No. 1107/2009 (4) (SANCO/10597/2003 rev. 10.1)
- CropLife International, 2009. Technical Monograph N o 17. Guidelines for Specifying the Shelf Life of Plant Protection Products.
- FAO. Guidelines for the packaging and storage of pesticides

Volume 3 Annex B5: Methods of Analysis

- EU guidance document on analytical methods for the analysis of technical material and preparation (SANCO/3030/99 rev. 4)
- EU guidance document on analytical methods for the determination of residues (Post-registration monitoring and control) (SANCO/825/00 rev. 8.1, 2010)
- EU guidance document for generating and reporting methods of analysis in support of pre-registration data requirements (SANCO/3029/99 rev. 4).
- OECD (2007). Guidance Document on Pesticide Residue Analytical Methods. Environment, Health and Safety Publications. Series on Testing and Assessment No. 72 and Series on Pesticides No. 39.

Volume 3 Annex B7: Residues

- OECD (2009). Guidance Document on Overview of Residue Chemistry Studies (as revised in 2009). Environment, Health and Safety Publications. Series on Testing and Assessment No. 64 and Series on Pesticides No. 32.
- OECD (2011) Guidance Document on Crop Field Trials (Series on Testing and Assessment No. 164 and Series on Pesticides No. 66)
- OECD (2008). Guidance document on magnitude of pesticide residues in processed commodities. Environment, Health and Safety Publications. Series on Testing and Assessment No. 96.
- OECD (2009). Guidance Document on the Definition of Residues. Environment, Health and Safety Publications. Series on Testing and Assessment No. 63 and Series on Pesticides No. 31
- EU guidance document "Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs" (SANCO 7525/VI/95 rev. 9, March 2011).
- OECD MRL calculator (2011)
- EU guidance document "Calculation of Maximum Residue Levels and Safety Intervals e.g. Pre-harvest Intervals" (SANCO 7039/VI/95, 22/7/1997)
- EFSA calculation model Pesticide Residue Intake Model "PRIMo" - revision 2
- For the PPP (Residues in or on Treated products, Food and Feed) Guidance documents reported in Section 6 of the Annex to Regulation (EU) No 283/2013 apply.

Volume 3 Annex B9: Ecotoxicology:

- Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC, SANCO/10329/2002, rev 2 (final) 17 October 2002;
- Guidance Document on Aquatic Ecotoxicology in the context of Directive 91/414/EEC, SANCO/3268/2001 rev 4 (final) 17 October 2002;
- Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters, EFSA Journal 2013;11(7):3290 (**Draft document**);
- European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals, EFSA Journal 2009; 7(12):1438.
- Candolfi et al.: Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods; ESCORT 2 workshop (European Standard Characteristics of Non-Target Arthropod Regulatory Testing), Wageningen, NL, 21-23 March 2000, SETAC Europe, SETAC publication August 2001.

Appendix V

APPENDIX V: SPECIFIC REFERENCES USED IN THIS ASSESSMENT

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

REFERENCE LIST

List [in the conventional format] any references specifically cited in Volume 1 (i.e. references to underpinning documents such as PPR-Panel Opinions, EFSA conclusions, national documents etc.).

Volume 3 Annex B2: Physicochemical properties

- FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) (2010), Manual on Development and use of FAO and WHO specifications for pesticides Second Revision

Volume 3 Annex B5 Analytical methods

None

Volume 3, Annex B6 Toxicology and Metabolism

- California Environmental Protection Agency, Air Resources Board (1998). Report for the application and ambient air monitoring for chlorpyrifos (and the oxon analogue) in Tulare County during spring/summer 1996.
- Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992, 2007 version. ("UK POEM").
- Lloyd G.A. and Bell G.J. (1983). Hydraulic nozzles: comparative spray drift study (MAFF/ADAS).
- Rautmann, D., Streloke, M. and Winkler, R. (2001). New basic drift values in the authorisation procedure for plant protection products. In Forster, R. and Streloke, M. Workshop on risk assessment and risk mitigation measures in the context of the authorisation of plant protection products (WORMM). Mitt. Biol. Bundesanst. Land-Forstwirtschaft. Berlin-Dahlem, Heft 381.
- Series 875, Occupational and Residential Exposure Test Guidelines: Group B – Postapplication Exposure Monitoring Test Guidelines (v 5.4, February 1998). USA EPA, Science Advisory Council for Exposure Policy 12, (February 2001): Recommended Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessment, USA EPA and Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment (August 1999 Presentation to the FIFRA Scientific Appraisal Panel), US EPA.
- Van Hemmen et al (2002). Post-application exposure of workers to pesticides in agriculture. Report of the re-entry working group, EUROPOEM II project: FAIR3-CT96-1406
- Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land-und Forstwirtschaft, Berlin-Dahlem, Heft 277, 1992. ('German Model').

Volume 3 Annex B7 Residues

- Gregory, J., Foster, K., Tyler, H. and Wiseman, M. (1990), The Dietary and Nutritional Survey of British Adults. HMSO
- Report on Health and Social Subjects, No. 36: 'The Diets of British Schoolchildren', HMSO
- Mills, A and Tyler, H. (1992), Food and Nutrient Intakes of British Infants Aged 6-12 months. HMSO
- Rees, N and Harris, C. (1995), UK Methods for the Estimation of Dietary Intakes of Pesticide Residues (unpublished)
- EFSA (2012), Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment, EFSA Journal 2012;10(07):2799

Volume 4, Annex C

None

Appendix VI

APPENDIX VI: RELEVANCE OF METABOLITES IN GROUNDWATER

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

Relevance of metabolites occurring in groundwater

In the environmental fate and behaviour section of this draft assessment report it was concluded that XDE-729 methyl and its two main soil metabolites X11393729 and X11449757 were not predicted to exceed 0.1 µg/l annual average at 1m depth in any of the FOCUS Groundwater scenarios. Therefore, an assessment of relevance in line with the requirements of the Guidance Document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC SANCO/221/2000 – rev.10 final, 25 February 2003 is required.

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Appendix VII

APPENDIX VII: LIST OF END POINTS

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis
Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Halauxifen-methyl
Function (e.g. fungicide)	Herbicide
Rapporteur Member State	UK
Co-rapporteur Member State	France

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	Methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate. (4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylic acid methyl ester using older software)
Chemical name (CA) ‡	2-pyridinecarboxylic acid, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-, methyl ester
CIPAC No ‡	Not available
CAS No ‡	943831-98-9
EC No (EINECS or ELINCS) ‡	Not available
FAO Specification (including year of publication) ‡	There is no FAO specification for XDE-729 Methyl.
Minimum purity of the active substance as manufactured ‡	93.0% (930 g/kg) (based on pilot scale material).
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	None
Molecular formula ‡	C ₁₄ H ₁₃ Cl ₂ FN ₂ O ₃
Molecular mass ‡	347.17 g/mol

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

XDE 729 Methyl (Halauxifen-methyl)

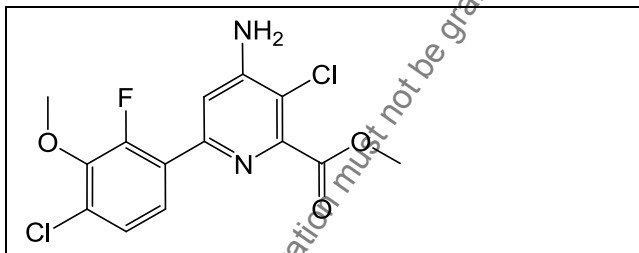
Volume 1, Level 3, Appendix VII

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

**Identity, Physical and Chemical Properties, Details of Uses, Further Information,
Methods of Analysis**

Structural formula ‡



‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

**Identity, Physical and Chemical Properties, Details of Uses, Further Information,
Methods of Analysis**

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	145.5 °C (99.1%)
Boiling point (state purity) ‡	Decomposes before boiling
Temperature of decomposition (state purity)	221.06 °C (99.1%)
Appearance (state purity) ‡	Pure Active Ingredient (99.1%) - White powder at 24.2°C
	Technical Grade Active Ingredient (95.1%) – Off-white powder at 23.8°C
Vapour pressure (state temperature, state purity) ‡	1.5×10^{-8} Pa at 25°C (1.1×10^{-10} mm Hg) and 5.9×10^{-9} Pa at 20°C (4.4×10^{-11} mm Hg). (Purity 99.1%)
Henry's law constant ‡	Unbuffered pH = 1.11×10^{-6} Pa m ³ /mol pH 5 = 1.23×10^{-6} Pa m ³ /mol pH 7 = 1.22×10^{-6} Pa m ³ /mol pH 9 = 1.20×10^{-6} Pa m ³ /mol (Calculated from water solubility and vp (units Pa m ³ mol ⁻¹))
Solubility in water (state temperature, state purity and pH) ‡	1.83 mg/L at 20°C (purified water), 1.66 mg/L at 20°C (pH 5), 1.67 mg/L at 20°C (pH 7), 1.69 mg/L at 20°C (pH 9) (99.1% pure).

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

**Identity, Physical and Chemical Properties, Details of Uses, Further Information,
Methods of Analysis**

Solubility in organic solvents ‡
(state temperature, state purity)

At 20°C (95.1%):
Methanol: 38.1 mg/L
Acetone: > 250 mg/L
Xylene: 9.13 mg/L
1,2-dichloromethane: 65.9 mg/L
Ethyl acetate: 129 mg/L
n-heptane: 0.0361 mg/L
n-octanol: 9.83 mg/L

Surface tension ‡
(state concentration and temperature, state purity)

The surface tension of a 90% saturated solution of XDE-729 Methyl TGAI (95.1% pure) was found to be **72.5 mN/m at 20°C.**

(For information, the notifier has informed the RMS that they intend to determine the surface tension using the pure active substance, the result of which should be available by the end of December 2013).

Partition co-efficient ‡
(state temperature, pH and purity)

log $P_{O/W}$ = 3.75 at 20°C at pH 5
log $P_{O/W}$ = 3.76 at 20°C at pH 7
log $P_{O/W}$ = 3.92 at 20°C at pH 9
(99.1% pure)

Given that the log K_{OW} > 3, the data suggests a potential to be fat soluble.

Dissociation constant (state purity) ‡

pK_{a1} = 2.84 ± 0.04 at 19.9°C (99.1%)

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

**Identity, Physical and Chemical Properties, Details of Uses, Further Information,
Methods of Analysis**

UV/VIS absorption (max.) incl. ϵ ‡
(state purity, pH)

λ max, nm
Neutral: 212, 249
Acidic: 215, 256
Basic: 212, 247
$L \text{ mol}^{-1} \text{ cm}^{-1}$
Neutral: 16,401-16,724 at 212 nm, 18,956-19,548 at 249 nm
Acidic: 22,496-22,516 at 215 nm, 23,770-23,779 at 256 nm
Basic: 19,023-19,099 at 212 nm, 21,979-22,061 at 247 nm
The molar absorption coefficients at the solar cut-off wavelength at 290 nm are shown below: pH < 2 : 12,474 $L \text{ mol}^{-1} \text{ cm}^{-1}$ pH 7 : 3,798 $L \text{ mol}^{-1} \text{ cm}^{-1}$ pH > 10 : 4,337 $L \text{ mol}^{-1} \text{ cm}^{-1}$
Determined at $25 \pm 0.5^\circ\text{C}$ (99.1% pure)
Flammability: Not highly flammable (95.1%, 92/69/EEC Method A.10) Auto flammability: No self-ignition temperature under the conditions of the test (up to a maximum temperature of 400°C). (95.1%, 92/69/EEC Method A.16).
Not explosive (95.1%, 92/69/EEC Method A.14).
Not oxidising (95.1%, 92/69/EEC Method A.17).

Flammability ‡ (state purity)

Explosive properties ‡ (state purity)

Oxidising properties ‡ (state purity)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

XDE 729 Methyl (Halauxifen-methyl)

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

**Identity, Physical and Chemical Properties, Details of Uses, Further Information,
Methods of Analysis**

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State Month and year

Active Substance (Name)

United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)
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Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Summary of representative uses evaluated (name of active substance or the respective variant)*

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		

Northern Zone

Winter cereals (soft wheat, barley, rye, triticale)	Northern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 09 to 29 (Sep 1st-Dec 31st) and BBCH 13 to 45 (March 1 st -Jun 20th)	2	0.00196-0.00782 followed by 0.00156 – 0.00625	100-400	0.00782 followed by 0.00625		"The applications are made in autumn only, or in spring only or in both autumn and spring. Autumn applications are from BBCH 09 to 29, from Sept 1st to Dec 31st. Spring applications are from BBCH 13 to 45, from March 1st to June 20th.
Spring cereals (wheat, barley)	Northern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 13 to 45 (March 1 st – Jun 20th)	1	0.00156 – 0.00625	100-400	0.00625		The application is made in spring only, from BBCH 13 to 45, from March 1st to June 20th

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State Month and year

Active Substance (Name)

United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)
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Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		

Central Zone

Winter cereals (soft wheat, durum wheat, barley, spelt, rye, triticale)	Central Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 09 to 29 (Sep 1st- Dec 31st) and BBCH 13 to 45 (Jan 1st - Jun 30th)	2	0.00196-0.00782 followed by 0.00156 – 0.00625	100-400	0.00782 followed by 0.00625		The applications are made in autumn only, or in spring only or in both autumn and spring. Autumn applications are from BBCH 09 to 29, from Sept 1st to Dec 31st. Spring applications are from BBCH 13 to 45, from January 1st to June 30th
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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State Month and year

Active Substance (Name)

United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)
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Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Spring cereals (wheat, barley, durum wheat, rye)	Central Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 13 to 45 (Feb 1st- Jun 30th)		0.00156 – 0.00625	100-400	0.00625		The application is made in spring only, from BBCH 13 to 45, from February 1st to June 30th
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‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State Month and year

Active Substance (Name)

United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)
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Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		

Southern Zone

Winter cereals (soft wheat, durum wheat, barley, spelt, rye, triticale)	Southern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 09 to 29 (Sep 1st-Dec 31st) and BBCH 13 to 45 (Jan 1st - May 31 st)	2	0.00196-0.00782 followed by 0.00156 – 0.00625	100-400	0.00782 followed by 0.00625		The applications are made in autumn only, or in spring only or in both autumn and spring. Autumn applications are from BBCH 09 to 29, from Sept 1st to Dec 31st. Spring applications are from BBCH 13 to 45, from January 1st to May 31 st
Spring cereals (wheat, barley, durum wheat, rye)	Southern Zone	GF-2573	F	Broadleaf weeds	EC	XDE-729 methyl 7.817	Overall, Broadcast foliar spray	BBCH 13 to 45 (Feb 1st-May 31 st)	1	0.00156 – 0.00625	100-400	0.00625		'The application is made in spring only, from BBCH 13 to 45, from February 1st to May 31 st

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

- (a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
- (b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
- (c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
- (d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
- (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
- (f) All abbreviations used must be explained
- (g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
- (h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
- (i) g/kg or g/l
- (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
- (k) Indicate the minimum and maximum number of application possible under practical conditions of use
- (l) PHI - minimum pre-harvest interval
- (m) Remarks may include: Extent of use/economic importance/restrictions

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Methods of Analysis

Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	HPLC-UV (270 nm)
Impurities in technical as (analytical technique)	HPLC-UV (270 nm), GC-FID
Plant protection product (analytical technique)	HPLC-UV (300 nm)

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin	XDE-729 methyl and XDE-729 acid
Food of animal origin	XDE-729 methyl and XDE-729 acid
Soil	XDE-729 methyl ester and its metabolites, XDE-729 acid and X11449757 (to be confirmed following peer review)
Water surface	XDE-729 methyl ester and its metabolites, XDE-729 acid, X11449757, and X11406790 (to be confirmed following peer review)
drinking/ground	XDE-729 methyl ester and its metabolites, XDE-729 acid, X11449757, and X11406790 (to be confirmed following peer review)
Air	XDE-729 methyl ester and XDE-729 acid (to be confirmed following peer review)

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Methods of Analysis

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)

Single method: LC/MS/MS, LOQ = 0.01 mg/kg (turnip root and wheat forage (wet crops), barley (grain, hay and straw) and wheat (grain, hay and straw) (dry crops), canola seed and sobean (oily crops), apple (whole) and orange (whole) (acidic crops), aspirated grain, bran bread, flour, germ, gluten, shorts and starch.

NB. The method relies on mixed stable isotope labelled internal standards.

QuEChERS Multi-Residue Method:
LC/MS/MS, LOQ = 0.01 mg/kg (kale leaves (wet crops), barley grain (dry crops), oilseed rape seed (oily crops) and lemon (acidic crops).

N.B. although mean recoveries in acidic matrices (lemon) and wet matrices (cabbage) were acceptable for the QuEChERS method, it is noted that the individual recoveries were occasionally low.

Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)

Single method: LC/MS/MS, LOQ = 0.01 mg/kg (bovine muscle, liver, kidney, fat, whole milk and cream and poultry muscle, liver, fat and eggs).

NB. The method relies on mixed stable isotope labelled internal standards.

QuEChERS Multi-Residue Method:
LC/MS/MS, LOQ = 0.01 mg/kg (bovine muscle, kidney, liver, fat and whole milk and poultry muscle and eggs).

N.B. extraction efficiencies have not been addressed as part of the method validation discussed above; however, residues are not expected to be found in products of animal origin for the proposed use. This will need to be addressed in future however if new uses give rise to positive residues.

Soil (analytical technique and LOQ)

LC/MS/MS, LOQ = 0.05 µg/kg (for XDE-729 methyl ester, XDE-729 acid and X11449757).

NB. The method relies on mixed stable isotope labelled internal standards.

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Methods of Analysis

Water (analytical technique and LOQ)

LC/MS/MS, LOQ = 0.05 µg/L (for XDE-729 methyl ester, XDE-729 acid, X11449757, and X11406790).

NB. The method relies on mixed stable isotope labelled internal standards.

Air (analytical technique and LOQ)

LC/MS/MS, LOQ = 0.82 µg/m³ (for XDE-729 methyl ester and XDE-729 acid).

Body fluids and tissues (analytical technique and LOQ)

XDE-729 Me is not classified as toxic or highly toxic; therefore monitoring methods for human tissues and body fluids are not required.

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

Active substance

RMS/peer review proposal

None

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Mammalian toxicology

Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1)

Rate and extent of oral absorption ‡	XDE-729 Acid (750 mg/kg bw/day, 10 mg/kg bw/day) and XDE-729 Methyl (10 mg/kg bw/day) are rapidly (< 24 hr) and completely (68-92%) absorbed.
Distribution ‡	XDE-729 Methyl and XDE-729 Acid undergo widespread systemic circulation, although there is no evidence of preferential distribution to any particular tissue.
Potential for accumulation ‡	No evidence of accumulation of XDE-729 Methyl or XDE-729 Acid.
Rate and extent of excretion ‡	XDE-729 Methyl and XDE-729 Acid are rapidly (< 24 hrs) and extensively (~100% for oral exposure) eliminated in urine (68-92%) and faeces (11-99%).
Metabolism in animals ‡	The main metabolite of XDE-729 Methyl is the hydrolysis product, XDE-729 Acid (X11393729, accounting for ~80% of dose). Minor metabolites of XDE-729 Methyl are an acyl-glucuronide conjugate of XDE-729 Acid (~6%), o-demethylated XDE-729 Acid (X11449757) and the corresponding sulfate and glucuronide conjugates (~6% of dose), and a glucuronide conjugate of o-demethyl XDE-729 Methyl (X11406790, up to 5.5% of dose at 3 mg/kg bw/day).
Toxicologically relevant compounds ‡ (animals and plants)	XDE-729 Acid at relevant human exposure levels
Toxicologically relevant compounds ‡ (environment)	XDE-729 Acid at relevant human exposure levels

Acute toxicity (Annex IIA, point 5.2)

Rat LD ₅₀ oral ‡	XDE-729 Methyl and XDE-729 Acid : >5000 mg/kg bw (rat)	
Rat LD ₅₀ dermal ‡	XDE-729 Methyl and XDE-729 Acid : >5000 mg/kg bw (rat)	
Rat LC ₅₀ inhalation ‡	Not determined (the generation of a respirable atmosphere is not technically possible)	
Skin irritation ‡	XDE-729 Methyl and XDE-729 Acid are not irritating	
Eye irritation ‡	XDE-729 Methyl and XDE-729 Acid are not	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Mammalian toxicology

Skin sensitisation ‡

irritating	
XDE-729 Methyl and XDE-729 Acid are not skin sensitisers (negative in LLNA)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡

XDE-729 Methyl: liver: increased liver weight, hypertrophy, fatty vacuolation, increased cholesterol; kidney – hypertrophy of collecting ducts; thyroid – increased thyroid weight, thyroid follicular cell hypertrophy; thymus – decreased thymus weight, atrophy (rats) attributed to stress

XDE-729 Acid: kidney tubule degeneration and regeneration (rats and dogs) and vacuolization of collecting duct (rats); hematopoietic hyperplasia of bone marrow, spleen and liver (dogs); bladder hyperplasia (male mice)

Relevant oral NOAEL ‡

XDE-729 Methyl: 5.78 mg/kg bw/day (based on increased liver weight and minor liver histopathological changes in mothers at 18.5 mg/kg/day in rabbit developmental toxicity study)

XDE-729 Acid: 11 mg/kg bw/day (based on slight tubular degeneration and regeneration in kidneys at 80 mg/kg bw/day in 28-day dog study)

Relevant dermal NOAEL ‡

XDE-729 Acid: 1000 mg/kg bw/day, the highest dose level tested

Relevant inhalation NOAEL ‡

Not applicable

Genotoxicity ‡ (Annex IIA, point 5.4)

XDE-729 Methyl and XDE-729 Acid: negative in *in vitro* and *in vivo* studies

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Mammalian toxicology**Long term toxicity and carcinogenicity (Annex IIA, point 5.5)**

Target/critical effect ‡

XDE-729 Methyl: liver toxicity, based on findings in short-term studies

XDE-729 Acid: kidney tubule degeneration and regeneration and necrosis, bladder hyperplasia and chronic inflammation in males (rats); kidney tubule degeneration and regeneration, bladder calculi, hyperplasia, and sub-acute to chronic inflammation in males (mice)

Relevant NOAEL ‡

XDE-729 Methyl: 5.78 mg/kg bw/day, based on findings in short-term studies

XDE-729 Acid: 50 mg/kg bw/day, 18 month mouse study

Carcinogenicity ‡

XDE-729 Methyl: not carcinogenic (conclusion applicable to oral dose levels of up to 10 mg/kg bw/day)

XDE-729 Acid: not carcinogenic

Reproductive toxicity (Annex IIA, point 5.6)**Reproduction toxicity**

Reproduction target / critical effect ‡

XDE-729 Methyl and XDE-729 Acid: None

Relevant parental NOAEL ‡

XDE-729 Acid : 98 mg/kg bw/day

Relevant reproductive NOAEL ‡

XDE-729 Acid: 443 mg/kg bw/day, the highest dose level tested (conclusion applicable to XDE-729 Methyl)

Relevant offspring NOAEL ‡

XDE-729 Acid: 443 mg/kg bw/day, the highest dose level tested (conclusion applicable to XDE-729 Methyl)

Developmental toxicity

Developmental target / critical effect ‡

XDE-729 Methyl and XDE-729 Acid: slight ossification delay or reduced foetal weight at maternally toxic dose levels

Relevant maternal NOAEL ‡

XDE-729 Methyl: 5.78 mg/kg bw/day (based on increased liver weight and minor liver histopathological changes in mothers at 18.5 mg/kg/day in rabbit developmental toxicity study)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Mammalian toxicology

Relevant developmental NOAEL ‡

XDE-729 Methyl: 18 mg/kg bw/day (rabbits) XDE-729 Acid: 159 mg/kg/day (rat)	
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Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡

XDE-729 Methyl: no evidence of neurotoxicity in general toxicity studies XDE-729 Acid: no evidence of neurotoxicity in special study or general toxicity studies	
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Repeated neurotoxicity ‡

XDE-729 Methyl: no evidence of neurotoxicity in general toxicity studies XDE-729 Acid: no evidence of neurotoxicity no evidence of neurotoxicity in special study or general toxicity studies	
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Delayed neurotoxicity ‡

Not relevant	
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Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡

A series of mechanistic investigations indicate that XDE-729 Methyl induces liver effects in rodents via an AhR-mediated mode of action

Studies performed on metabolites or impurities ‡

O-demethyl XDE-729 Acid (X11449757) tested negative in <i>in vitro</i> assays for gene mutation and clastogenicity
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Medical data ‡ (Annex IIA, point 5.9)

No medical data are available

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Mammalian toxicology

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.058 mg/kg bw/day	XDE-729 Methyl dietary rabbit developmental toxicity study	100
AOEL ‡	0.058 mg/kg bw/day	XDE-729 Methyl dietary rabbit developmental toxicity study	100
ARfD ‡	2.5 mg/kg bw/day	XDE-729 Acid oral (gavage) acute neurotoxicity study	100

Dermal absorption ‡ (Annex IIIA, point 7.3)

Formulation (GF-2573 (EC), containing 7.6 g/L XDE-729 Methyl)

1% for the concentrate, 4% for field dilution of 0.12-0.15 g a.i./L, 15% for field dilution of 0.02-0.025 g a.i./L

Exposure scenarios (Annex IIIA, point 7.2)

Operator

- UK POEM¹ - The predicted operator exposure is calculated to be equivalent to 15% of the AOEL for XDE-729 methyl for an operator wearing no PPE.
- German Model² - The predicted operator exposure is calculated to be equivalent to 1% of the AOEL for XDE-729 methyl for an operator wearing no PPE.

¹ Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992, 2007 version. ("UK POEM").

Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land-und Forstwirtschaft, Berlin-Dahlem, Heft 277, 1992. ('German Model').

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Mammalian toxicology

Workers

- Worker exposure estimates were calculated using the EUROPOEM II worker re-entry model³. The predicted exposure for a worker without personal protective equipment is calculated to be equivalent to 2% of the AOEL for XDE-729 methyl

Bystanders

- Bystander exposure to vapour was estimated using a surrogate value derived from Californian Environmental Protection Agency studies⁴. The predicted bystander exposure to vapour is calculated to be 7% of the AOEL for an adult and 14% of the AOEL for a child for XDE-729 methyl.
- Bystander exposure to spray drift was estimated using measurements of simulated bystander exposure for field crop sprayers in a UK study⁵. The predicted bystander exposure to spray drift was calculated to be equivalent to <1% of the AOEL for XDE-729 methyl.
- Bystander exposure to fallout (children model) was calculated to be equivalent to <1% of the AOEL for XDE-729 methyl.

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

Substance classified (XDE-729 Methyl)

RMS/peer review proposal

No classification required in relation to toxicology data

³ van Hemmen et al (2002). Post-application exposure of workers to pesticides in agriculture. Report of the re-entry working group, EUROPOEM II project: FAIR3-CT96-1406

⁴ California Environmental Protection Agency, Air Resources Board (1998). Report for the application and ambient air monitoring for chlorpyrifos (and the oxon analogue) in Tulare County during spring/summer 1996.

⁵ Lloyd G.A. and Bell G.J. (1983). Hydraulic nozzles: comparative spray drift study (MAFF/ADAS).

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues**Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)**

Plant groups covered	Wheat and Turnip, representing cereal and root crops.
Rotational crops	Wheat, radish and lettuce, representing cereal, root and leafy vegetable crops.
Metabolism in rotational crops similar to metabolism in primary crops?	Due to the low residue levels (all crop fractions harvested contained less than 0.01 mg/kg XDE-729 methyl equivalents) in all crops at all plant-back intervals, a metabolic pathway has not been proposed.
Processed commodities	XDE-729 methyl is degraded with formation of one degradate, X11393729, under conditions representative of pasteurisation, baking, brewing, boiling and sterilisation. X11393729 can be regarded as stable to hydrolysis.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Yes, the residues present in both processed commodities and RACs are defined as XDE-729 methyl and XDE-729 acid.
Plant residue definition for monitoring	XDE-729 methyl and XDE-729 acid
Plant residue definition for risk assessment	XDE-729 methyl and XDE-729 acid
Conversion factor (monitoring to risk assessment)	None

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Hen (poultry), Goat (Ruminant)
Time needed to reach a plateau concentration in milk and eggs	Milk: 3 days Eggs: A definite plateau was not reached; However, due to the low level of residues found (max ca. 0.003 mg/kg XDE-729 methyl equivalents) and given the study was conducted at 625 times the maximum theoretical burden to hens, it was concluded that despite not reaching the plateau, the study was fit for purpose to support the proposed GAP.
Animal residue definition for monitoring	XDE-729 methyl and XDE-729 acid

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

Animal residue definition for risk assessment

XDE-729 methyl and XDE-729 acid

Conversion factor (monitoring to risk assessment)

None

Metabolism in rat and ruminant similar (yes/no)

Yes

Fat soluble residue: (yes/no)

Given that the $\log K_{ow} > 3$ for XDE-729 methyl, the data suggests a potential to be fat soluble.

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Confined rotational crop metabolism study demonstrated that it is unlikely that crops rotated into wheat fields treated with XDE-729 at 10 g a.s./ha would result in detectable levels of XDE-729 methyl or metabolites in any Raw Agricultural Commodity. Because of the low residue levels in all crops at all plant-back intervals, a metabolic pathway has not been proposed, and a succeeding crop study and tolerance/MRL are not necessary for succeeding crops.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

Plant Matrices

The frozen storage stability of XDE 729 methyl ester and its major metabolite XDE 729 acid have been determined in lettuce (a high-water crop), wheat grain (a dry crop), oilseed rape seed (an oily crop), and oranges (a high-acid crop) as part of an ongoing 24 month study. Data has been collected to approximately 16 months and indicates that residues of XDE 729 methyl ester and XDE 729 acid are stable, with no observable degradation.

Animal Tissues

The frozen storage stability of XDE 729 methyl ester and its major metabolites, XDE 729 acid and X11449757, have been determined in ruminant and poultry tissues as part of an ongoing 24 month study.

For XDE 729 methyl ester and XDE 729, data has been collected to approximately 12 months for bovine muscle, bovine milk, poultry liver, and poultry eggs, and indicates that XDE 729 methyl ester and XDE 729 acid are stable, with no observable degradation.

For X11449757, data has been collected to approximately 6 months for bovine muscle, bovine milk, poultry liver, and poultry eggs, and indicates that X11449757 is stable, with no observable degradation.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes,

Ruminant:	Poultry:	Pig:
Conditions of requirement of feeding studies		
No	No	No

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

specify the level)

Potential for accumulation (yes/no):

Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)

Muscle

Liver

Kidney

Fat

Milk

Eggs

Given that the $\log K_{OW} > 3$ for XDE-729 methyl, the data suggests a potential to be fat soluble.	Given that the $\log K_{OW} > 3$ for XDE-729 methyl, the data suggests a potential to be fat soluble.	Given that the $\log K_{OW} > 3$ for XDE-729 methyl, the data suggests a potential to be fat soluble.
No	No	No
*Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Not applicable*	Not applicable*	Not applicable*
Not applicable*	Not applicable*	Not applicable*
Not applicable*	Not applicable*	Not applicable*
Not applicable*	Not applicable*	Not applicable*
Not applicable*		
	Not applicable*	

* There is no requirement for animal feeding studies for the EU. However, feeding studies were carried out to address the higher level of residues found in the Australian residue trials. This data has not been relied upon for the current evaluation, and hence values have not been presented in the table above; however, the feeding study was evaluated and presented in the DAR for completion, therefore please refer to the residue section of the DAR for details.

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendations	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Winter Wheat	Northern	Grain: all samples <0.02 (n=11) Straw: all samples <0.02 (n=11)	MRL for XDE-729 methyl of 0.02 mg/kg is proposed for the following cereal grains: barley (including spring and winter barley) and by extrapolation wheat, to include spring wheat, winter wheat, soft wheat, durum wheat, triticale and spelt), and rye.	0.02	0.02 (Grain and Straw)	0.02 (Grain and Straw)
Winter Barley	Northern	Grain: all samples <0.02 (n=10) Straw: all samples <0.02 (n=10)	As above	0.02	0.02 (Grain and Straw)	0.02 (Grain and Straw)
Spring Wheat	Northern	Grain: all samples <0.02 (n=10) Straw: 9 samples <0.02, one sample 0.026 (n=10)	As above	0.02	0.02 (Grain) 0.026 (straw)	0.02 (Grain and straw)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

Spring Barley	Northern	Grain: all samples <0.02 (n=11) Straw: all samples <0.02 (n=11)	As above	0.02	0.02 (Grain and Straw)	0.02 (Grain and Straw)
Winter Wheat	Southern	Grain: all samples <0.02 (n=11) Straw: all samples <0.02 (n=11)	As above	0.02	0.02 (Grain) 0.02 (Straw)	0.02 (Grain and Straw)
Winter Barley	Southern	Grain: all samples <0.02 (n=11) Straw: 10 samples <0.02, one sample at 0.05 (n=11)	As above	0.02	0.02 (Grain) 0.05 (Straw)	0.02 (Grain and Straw)
Spring Wheat	Southern	Grain: all samples <0.02 (n=9) Straw: 8 samples <0.02, one sample 0.03 (n=9)	As above	0.02	0.02 (Grain) 0.03 (Straw)	0.02 (Grain and Straw)
Spring Barley	Southern	Grain: all samples 0.02 (n=9*) Straw: 8 samples <0.02, one sample 0.025) (n=9*)	As above *ten trials were submitted; however, one trial (Bulgarian trial, CEMS-4720G) was considered to be an outlier, and therefore was not relied on.	0.02	0.02 (Grain) 0.025 (Straw)	0.02 (Grain and Straw)

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17

(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use

(c) Highest residue

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.058 mg/kg bw/day
TMDI (% ADI) according to WHO European diet	N/A – see IEDI
TMDI (% ADI) according to national (to be specified) diets	<1 % (all Member States) [Primo rev. 2]
IEDI (European Diet) (% ADI)	0.3% (DK child)
NEDI (specify diet) (% ADI)	<1% (UK diet; all sub-populations)
Factors included in IEDI and NEDI	Not applicable
ARfD	2.5 mg/kg bw/day
IESTI (% ARfD)	<1%
NESTI (% ARfD) according to national (to be specified) large portion consumption data	<1% (UK diet; all sub-populations)
Factors included in IESTI and NESTI	Not applicable

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
Wheat/ cleaned grain, middlings, wheat germ, fine bran, coarse bran, total bran, refined flour, white bread, wholemeal bread and wholemeal flour.	3	Residues of XDE-729 methyl and XDE-729 acid in grain and all processed products from each of the three wheat and the three barley trials in treated as well as untreated samples were not detected (ND, <0.003 mg/kg).		
Barley/ cleaned grain, pot barley, barley bran, barley flour, brewing malt, malt sprouts, spent grain, flocs, brewer's yeast and beer.	3	These studies demonstrated that residues of XDE-		

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

		729 methyl are not expected to concentrate in processed fractions of grain.		

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Residues

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

.....	A MRL of 0.02 mg/kg is proposed for the following cereal grains: barley (including spring and winter barley) and by extrapolation wheat, to include spring wheat, winter wheat, soft wheat, durum wheat, triticale and spelt), and rye.
.....	
.....	
.....	
.....	

When the MRL is proposed at the LOQ this should be annotated by an asterisk after the figure.

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡

Non-sterile conditions:
 14.8 – 17.3 % after 104 d, [¹⁴C-Phenyl]-label (n⁶= 3)
 3.3 – 21.0 % after 104 d, [¹⁴C-Pyridine]-label (n= 4)

Sterile conditions:
 0.3 – 0.7 % after 62 d, [¹⁴C-Phenyl]-label (n= 4)
 0.6 – 1.0 % after 62 d, [¹⁴C-Pyridine]-label (n= 4)

Non-extractable residues after 100 days ‡

Non-sterile conditions:
 59.5 – 64.4 % after 104 d, [¹⁴C-Phenyl]-label (n= 3)
 62.5 – 82.5 % after 104 d, [¹⁴C-Pyridine]-label (n= 4)
 Note: one soil met regulatory trigger of >70% unextracted residue and <5% mineralisation at 104 days with Pyridine label.

Sterile conditions:
 0.0 – 6.7 % after 62 d, [¹⁴C-Phenyl]-label (n= 4)
 0.0 – 11.9 % after 62 d, [¹⁴C-Pyridine]-label (n= 4)

Metabolites requiring further consideration ‡
 - name and/or code, % of applied (range and maximum)

X11393729 – 38.2 – 72.7 % at 3 - 7 d (n= 4)
 X11449757 – 2.7 – 17.4 % at 3 - 14 d (n= 4)
 [¹⁴C-phenyl] & [¹⁴C-pyridine] labels

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡

Mineralization after 100 days

0.3 – 0.8 % after 100 d, [¹⁴C-Phenyl]-label (n=

⁶ n corresponds to the number of soils.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Non-extractable residues after 100 days	4) 0.3 – 0.7 % after 100 d, [¹⁴C-Pyridine]-label (n= 4) 21.9 – 48.6 % after 100 d, [¹⁴C-Phenyl]-label (n= 4) 19.1 - 47.4% after 100 d, [¹⁴C-Pyridine]-label (n= 4)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	X11393729 – 47.4 – 79.6 % at 0 - 14 days post flooding (n= 4) X11449757 – 25.7 – 54.3 % at 100 - 121 days post flooding (n= 4) [¹⁴C-phenyl] & [¹⁴C-pyridine] labels
Soil photolysis ‡	
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	X11393729 – 49.1 % at 15 d (n= 1) X11449757 – 6.8 % at 15 d (n= 1) [¹⁴C-phenyl] & [¹⁴C-pyridine] labels

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type	X ⁷	pH	t. °C / % MWHC	DT ₅₀ /DT ₉₀ (d)	DT ₅₀ (d) 20°C pF2/10kPa	St. (χ^2)	Method of calculation
Clay loam		7.1	20 °C / 50 %	1.8 / 16.3 2.0 / 6.7	1.8 / 16.3 2.0 / 6.7	3.3 18.3	FOMC - P SFO - M
Loam		5.0	20 °C / 50 %	1.3 / 4.5 1.3 / 4.5	1.1 / 3.7 1.1 / 3.7	8.4 8.4	SFO – P SFO - M
Silt loam		5.9	20 °C / 50 %	1.1 / 6.1 1.2 / 4.0	1.1 / 6.1 1.2 / 4.0	4.4 110.9	FOMC – P SFO - M
Sandy loam		7.5	20 °C / 50 %	0.9 / 3.8 0.9 / 3.0	0.9 / 3.8 0.9 / 3.0	7.0 9.3	SFO – P SFO – M
Silt loam		5.9	10 °C / 50%	2.2 / 12.2	-	4.9	FOMC - P
Geometric mean (SFO DT50 for modelling)					1.3		

P = persistence endpoint M = modelling endpoint

⁷ X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

X11393729	Aerobic conditions							
Soil type	X ¹	pH	t. °C / % MWHC	DT ₅₀ / DT ₉₀ (d)	f. f. k _{dp} / k _f	DT ₅₀ (d) 20°C pF2/10kPa	St. (%)	Method of calculation
Clay loam		7.1	20 °C / 50 %	35.9 / 119 28.7 / 95	0.63 72	35.9 / 119 28.7 / 95	6.0 16.4	TD SFO – P SFO IS - M
Loam		5.0	20 °C / 50 %	3.3 / 11 2.0 / 6.8	0.85 48	2.7 / 9 1.6 / 5.5	20.1 14.4	TD SFO – P SFO IS - M
Silt loam		5.9	20 °C / 50 %	7.6 / 25.4 4.7 / 15.8	0.77 33	7.6 / 25.4 4.7 / 15.8	13.1 14.4	TD SFO – P SFO IS - M
Sandy loam		7.5	20 °C / 50 %	13.6 / 45.2 11.7 / 38.9	0.77 53	13.6 / 45.2 11.7 / 38.9	11.3 14.7	TD SFO – P SFO IS - M
Silt loam		5.9	10 °C / 50%	21.0 / 69.6	-	-	10.0	TD SFO - P
Geometric mean (SFO DT50 for modelling)					0.76 02*	7.5		

P = persistence endpoint M = modelling endpoint TD = top down IS = in series

*arithmetic mean

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

X11449757	Aerobic conditions							
Soil type	X ¹	pH	t. °C / % MWHC	DT ₅₀ / DT ₉₀ (d)	f. f. k _{dp} / k _f	DT ₅₀ (d) 20°C pF2/10kPa	St. (%)	Method of calculation
Clay loam		7.1	20 °C / 50 %	76.7 / 255	1	76.7 / 255	5.2	TD SFO – P & M
Loam		5.0	20 °C / 50 %	25.1 / 84	1	20.4 / 68.4	17.0	TD SFO – P & M
Silt loam		5.9	20 °C / 50 %	31.8 / 106	1	31.8 / 106	13.8	TD SFO – P & M
Sandy loam		7.5	20 °C / 50 %	47.7 / 158	1	47.7 / 158	12.3	TD SFO – P & M
Geometric mean (SFO DT50 for modelling)					1	41.3		

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Field studies - Persistence endpoints

Parent				
Site	Season	Best fit model	DT50 (days)	DT90 (days)
Germany	Spring	SFO	18	60
	Autumn	FOMC	5	78
UK	Spring	SFO	43	144
	Autumn	FOMC	15	106
Spain	Spring	SFO	15	51
	Autumn	FOMC	11	86
France	Spring	SFO	15	49
	Autumn	DFOP	2.1	51
Worst case		SFO	43	144

X11393729 – top down				
Site	Season	Model	DT50 (days)	DT90 (days)
Germany	Spring	SFO	Not used	Not used
	Autumn	SFO	101.7	337.9
UK	Spring	SFO	264.4	871.7
	Autumn	SFO	163.5	543.2
Spain	Spring	SFO	62	207
	Autumn	SFO	108	359
France	Spring	SFO	17	56
	Autumn	SFO	44	145
Worst case		SFO	264.4	871.7

X11449757 – top down				
Site	Season	Model	DT50 (days)	DT90 (days)
Germany	Spring	SFO	Not used	Not used
	Autumn	SFO	197.0	654.4
UK	Spring	SFO	187.1	621.4
	Autumn	SFO	Not used	Not used
Spain	Spring	SFO	113.2	375.9
	Autumn	SFO	104.7	347.8
France	Spring	SFO	146.0	484.9
	Autumn	SFO	87.3	290.2
Worst case		SFO	197.0	654.4

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Site	Peak concentration of parent (DAT)	Molar observed formation of X11393729 (% DAT)	Molar observed formation of X11449757 (% DAT)
Germany Spring	3.51 µg/kg (0 DAT)	6.5% (13 DAT)	9.9% (91 DAT)
UK Spring	4.34 µg/kg (1 DAT)	18.3% (89 DAT)	2.0% (89 DAT)
Spain Spring	6.21 µg/kg (1 DAT)	37.1% (0 DAT); 17.1% (27 DAT)	12.6% (0 DAT); 3.3% (27 DAT)
France Spring	3.79 µg/kg (0 DAT)	14.0% (3 & 15 DAT)	9.2% (15 DAT)
Germany Autumn	4.23 µg/kg (1 DAT)	34.3% (62 DAT)	4.6% (62 DAT)
UK Autumn	4.97 µg/kg (7 DAT)	32.1% (29 DAT)	1.8% (180 DAT)
Spain Autumn	5.42 µg/kg (0 DAT)	21.7% (7 DAT)	2.0% (7 DAT)
France Autumn	3.07 µg/kg (0 DAT)	40.1% (3 DAT)	13.8% (31 DAT)

Field studies - Modelling endpoints

Modelling to derive XDE-729 methyl concentrations only				
Location	Season	Model	DT50 (d)	Chi ² Error (%)
Germany	Spring	SFO (after 10mm rain)	17	24
Germany	Autumn	SFO (after 10mm rain)	27	24
UK	Spring	SFO (after 10mm rain)	26	19
UK	Autumn	SFO (after 10mm rain)	8.2	20
Spain	Spring	SFO (after 10mm rain)	25	32
Spain	Autumn	SFO (after 10mm rain)	33	11
France	Spring	SFO (after 10mm rain)	17	15
France	Autumn	SFO (after 10mm rain)	19	19
Geomean			20	-
Average			22	-
Median			22	-

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Modelling to derive X11393729 ('Acid') concentrations only pH dependence to be accounted for in exposure assessment								
Location	Season	Parent + Acid (SFO+SFO)					Top-down SFO	
		Parent DT50 (d)	Chi ² Err (%)	Acid DT50 (d)	FF	Chi ² Err (%)	Acid DT50 (d)	Chi ² Err (%)
Germany	Spring	0.7*	28	23	0.12	34	59	32
Germany	Autumn	2.5	32	42	0.44	25	30	13
UK	Spring	27	28	35	0.66	33	88	6.5
UK	Autumn	1.1	40	51	0.36	14	59	9.5
Spain	Spring	6.4	17	34	0.33	49	62	15
Spain	Autumn	9.1	20	40	0.34	49	85	16
France	Spring	6.6	40	2.3	1.00	32	29	25
France	Autumn	0.7	27	41	0.34	61	28	36
Geomean		3.3	-	22	0.38	-	50	-
Average		6.8	-	30	0.45	-	55	-
Median		4.5	-	35	0.35	-	59	-

FF = formation fraction

* DFOP/SFO model used

Modelling to derive X11449757 ('X-757') concentrations only									
Location	Season	Parent + Acid + X-757 (SFO+SFO+ SFO)						Top-down SFO	
		Parent DT50	Acid DT50	Acid FF	X-757 DT50 (d)	X-757 FF	Chi ² Err (%)	X-757 DT50 (d)	Chi ² Err (%)
Germany	Spring	NC	NC	NC	NC	NC	NC	NC	NC
Germany	Autumn	1.9	43	0.41	8.9	1.00	16	76	4.6
UK	Spring	NC	NC	NC	NC	NC	NC	60	13
UK	Autumn	1.0	54	0.35	22	0.22	37	NC	NC
Spain	Spring	NC	NC	NC	NC	NC	NC	84	26
Spain	Autumn	NC	NC	NC	NC	NC	NC	60	12.6
France	Spring	5.8	1.9	1.00	73	0.18	36	107	21
France	Autumn	0.7	8.6	0.36	9.5	1.00	30	37	11
Geomean		1.7	14	0.48	19	0.45	-	67	-
Average		2.4	27	0.53	28	0.60	-	71	-
Median		1.5	26	0.39	16	0.61	-	68	-

FF = formation fraction NC = not calculated

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

pH dependence ‡
(yes / no) (if yes type of dependence)

XDE-729 methyl – no
X11393729 – yes, increasing DT₅₀ with increasing pH
X11449757 - no, (in lab, increasing DT₅₀ with increasing pH; no trend apparent in field)

Laboratory studies ‡

Parent	Anaerobic conditions						
Soil type	X ⁸	pH	t. °C / % MWHC	DT ₅₀ / DT ₉₀ (d)	DT ₅₀ (d) 20°C pF2/10k Pa	St. (χ ²)	Method of calculation
Clay loam		7.1	20 °C / 50 % for 1 day, flooded there- after	2.8 / 29	-	4.9	DFOP from day of flooding
Loam		5.0	20 °C / 50 % for 1 day, flooded there- after	1.6 / 5.5	-	10.3	SFO from day of flooding
Silt loam		5.9	20 °C / 50 % for 1 day, flooded there- after	0.9 / 3.1	-	9.3	SFO from day of flooding
Sandy loam		7.5	20 °C / 50 % for 1 day, flooded there- after	1.9 / 6.5	-	6.5	SFO from day of flooding
Geometric mean/median							

⁸ X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

X11393729	Anaerobic conditions							
Soil type	X ¹	pH	t. °C / % MWHC	DT ₅₀ / DT ₉₀ (d)	f. f. k _{dp} /k _f	DT ₅₀ (d) 20°C pF2/10k Pa	St. (%)	Method of calculation
Clay loam		7.1	20 °C / 50 % for 1 day, flooded there-after	77 / 257 90 / 299	0.9784	-	4.7 6.3	DFOP/SFO SFO TD
Loam		5.0	20 °C / 50 %% for 1 day, flooded there-after	21 / 70 21 / 70	2.3x10 ⁻¹⁴	-	4.3 4.6	SFO/SFO SFO TD
Silt loam		5.9	20 °C / 50 %% for 1 day, flooded there-after	14 / 46 21 / 69	0.8213	-	6.6 27.2	SFO/SFO SFO TD
Sandy loam		7.5	20 °C / 50 %% for 1 day, flooded there-after	106 / 352 100 / 334	1.0000	-	3.4 3.8	SFO/SFO SFO TD
Geometric mean/median								

*unrealistic optimised ff as peak on day of flooding TD = top down

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

X11449757	Anaerobic conditions							
Soil type	X ¹	pH	t. °C / % MWHC	DT ₅₀ / DT ₉₀ (d)	f. f. k _{dp} /k _f	DT ₅₀ (d) 20°C pF2/10k Pa	St. (%)	Method of calculation
Clay loam		7.1	20 °C / 50 % for 1 day, flooded there-after	92 / 304	0.6416	-	6.0	DFOP/SFO/ SFO
Loam		5.0	20 °C / 50 %% for 1 day, flooded there-after	165 / 549	0.9505	-	13.4	SFO/SFO/S FO
Silt loam		5.9	20 °C / 50 %% for 1 day, flooded there-after	127 / 421	0.7011	-	10.1	SFO/SFO/S FO
Sandy loam		7.5	20 °C / 50 %% for 1 day, flooded there-after	>1000 / >1000	0.7366	-	20.3	SFO/SFO/S FO
Geometric mean/median								

Top down kinetics not possible due to insufficient time points after peak, or peak not reached at study end.

Soil photolysis – degradation of XDE-729 methyl and X11393729 slower under illuminated conditions than under dark control conditions.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent: XDE-729 methyl‡							
Soil Type (USDA)	OC %	Soil pH	Kd (ml/g)	Koc (ml/g)	Kf (ml/g)	Kfoc (ml/g)	1/n
Clay loam	1.3	7.1	35	2659	24	1812	0.89
Loamy sand	1.1	5.2	25	2294	17	1553	0.88
Loam	2.5	5	39	1576	28	1104	0.90
Silt loam	3.6	5.9	36	1007	24	660	0.88
Sandy loam	1.4	7.5	13	893	9	652	0.89
Clay loam	4.4	7.2	21	473	8	190	0.76
Organic*	33.1	4.1	340	1026	310*	936*	0.98*
Arithmetic mean					18	995	0.87
pH dependence, Yes or No				Very weak, not considered in modelling			

* results excluded from calculation of mean as soil considered unrepresentative

Metabolite: X11393729‡							
Soil Type	OC %	Soil pH	Kd (ml/g)	Koc (ml/g)	Kf (ml/g)	Kfoc (ml/g)	1/n
Clay loam	1.3	7.1	2.23	172	1.48	113	0.83
Loamy sand	1.1	5.2	1.90	172	1.66	151	0.96
Loam	2.5	5	3.87	155	2.40	96	0.83
Silt loam	3.6	5.9	3.63	101	2.40	67	0.84
Sandy loam	1.4	7.5	0.58	41	0.41	29	0.88
Clay loam	4.4	7.2	1.50	34	1.14	26	0.88
Organic*	33.1	4.1	179	539	113*	341*	0.91*
Arithmetic mean/median				Not appropriate, pH dependence			
pH dependence (yes or no)				Yes, increased sorption at low pH			

* results excluded from consideration as soil considered unrepresentative

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite: X11449757‡							
Soil Type	OC %	Soil pH	Kd (ml/g)	Koc (ml/g)	Kf (ml/g)	Kfoc (ml/g)	1/n
Clay loam	1.3	7.1	2.59	200	1.84	142	0.87
Loamy sand	1.1	5.2	2.73	248	1.86	169	0.86
Loam	2.5	5	4.98	199	3.28	131	0.83
Silt loam	3.6	5.9	6.01	167	3.73	104	0.84
Sandy loam	1.4	7.5	0.34	24	0.26	19	0.90
Clay loam	4.4	7.2	0.76	17	0.66	15	0.95
Organic*	33.1	4.1	195	590	134*	405*	0.93*
Arithmetic mean/median		Not appropriate, pH dependence					
pH dependence (yes or no)			Yes, increased sorption at low pH				

* results excluded from consideration as soil considered unrepresentative

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡

Not submitted, not required

Aged residues leaching ‡

Not submitted, not required

Lysimeter/ field leaching studies ‡

Not submitted, not required

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

PEC (soil) (Annex IIIA, point 9.1.3)

Parent	DT ₅₀ (d): 43 days			
Method of calculation	Kinetics: SFO			
	Field or Lab: representative worst case from field studies.			
Application data	Crop: wheat Depth of soil layer: 5 cm Soil bulk density: 1.5 g/cm ³ % plant interception: 25% Number of applications: 2 Interval (d): 70 days Application rate(s): 1 x 7.82 g as/ha + 1 x 6.25 g a.s./ha			
PEC _(s) (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.008		0.009	
Short term 1d	0.008	0.008	0.009	0.009
2d	0.008	0.008	0.009	0.009
4d	0.007	0.008	0.008	0.009
Long term 14d	0.006	0.007	0.007	0.008
28d	0.005	0.006	0.006	0.007
50d	0.003	0.005	0.004	0.006
100d	0.002	0.004	0.002	0.004

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite X11393729

Method of calculation

Molecular weight relative to the parent: 0.959
 DT₅₀ (d): 264 days
 Kinetics: SFO
 Field or Lab: representative worst case from field studies.

Application data

Application rate assumed: total dose 5.11 g /ha
 (assumes a total dose of 14.02 g a.s./ha with 25% crop interception; X11393729 is formed at a maximum field study molar formation of 40.1 % of the applied dose)

PEC _(s) (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.005			
Short term				
2d				
4d				
Long term				
28d				
50d				
100d				
Plateau concentration	0.009 mg/kg after 6 yr			

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite X11449757

Method of calculation

Molecular weight relative to the parent: 0.919

DT₅₀ (d): 197 days

Kinetics: SFO

Field or Lab: representative worst case from field studies.

Application data

Application rate assumed: total dose 1.34 g /ha (assumes a total dose of 14.02 g a.s./ha with 25% crop interception; X11449757 is formed at a maximum field study molar formation of 13.8 % of the applied dose)

PEC _(s) (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.002			
Short term				
2d				
4d				
Long term				
28d				
50d				
100d				
Plateau concentration	0.0025 mg/kg after 5 yr			

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10 %, DT50 ‡

pH 4: 245 d at 10°C 80.9 d at 25°C 12.1 d at 50°C SFO, $r^2 > 0.99$ Met X11393729: max 8.1% at 10°C, 23.7% at 25°C, 83.3%AR at 50°C, all at study end (30 DAT)
pH 7: 660 d at 10°C 155 d at 25°C 17.1 d at 50°C SFO, $r^2 = 0.83 - 1.00$ Met X11393729: max 3.7% at 10°C, 13.0% at 25°C, 70.3%AR at 50°C, all at study end (30 DAT)
pH 9: 17.8 d at 10°C 3.04 d at 25°C 0.218 d at 50°C SFO, $r^2 = 1.00$ Met X11393729: max 72.0% at 30 DAT at 10°C, 99.3% at 30 DAT at 25°C, 99.6%AR at 21 DAT at 50°C

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Photolytic degradation of active substance and metabolites above 10 % ‡

Xenon lamp, 14 – 15 days continuous illumination equivalent to 34 – 36 days natural summer sunlight at 40°N

DT₅₀ sterile buffer: 4.1 minutes (SFO)

DT₅₀ natural water: 7.1 minutes (SFO)

Estimated DT₅₀ at 40°N in summer: 7.7 minutes in sterile buffer; 18.3 minutes in natural water.

Identified metabolites exceeding 10% AR (values are maximums in individual reps):

Deg 10: 12.6% AR (18 minutes, buffer)

Deg 11: 15.7% AR (18 minutes, buffer)

Deg 14: 11.5% AR (129 minutes, buffer)

X11393729: 10.7% AR (10 minutes, natural water)

Quantum yield of direct phototransformation in water at $\Sigma > 290$ nm

5.6 mol · Einstein⁻¹

Readily biodegradable ‡
(yes/no)

Study on metabolite X11393729, considered not readily biodegradable.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Degradation in water / sediment

Parent	Distribution (Max. sed 7.3 – 12.2 % after 2 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DegT ₅₀ - DegT ₉₀ whole sys.	St. (χ^2)	DisT ₅₀ - DisT ₉₀ water	St. (χ^2)	DisT ₅₀ - DisT ₉₀ sed	St. (r^2)	Method of calculatio n
Swiss Lake	7.0	5.8	20	4 / 12 days	9. 4	3 / 9 days	9. 2 (1 1)	7 / 24 days	16 .2	SFO (WS) SFO (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	0.8 / 2.9 days	1. 3	0.67 / 2.24 days	0. 1 (1 5. 9)	1.3 / 4.6 days	2. 1	SFO (WS) SFO (WP) SFO TD (SP)
Geometric mean				1.8 / 5.9						

WS = whole system WP = water phase TD = top down SP = sediment phase

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite X11393729	Distribution (max in water 13.3 – 20.0% after 2 - 8 d. Max. sed 3.2 – 6.1 % after 2-5 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT ₅₀ - DT ₉₀ whole sys.	St. (χ^2)	DisT ₅₀ - DisT ₉₀ water	χ^2	DisT ₅₀ - DisT ₉₀ sed	St. (χ^2)	Method of calculatio n
Swiss Lake	7.0	5.8	20	11 / 38 days (dissipati on)	20 .7	9 / 28 days	16 .1	4 / 14 days	2. 3	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	2 / 6.7 days (degradati on)	1. 3	3 / 10 days	4. 5	Not calculated Insufficie nt data		SFO IS (WS) SFO TD (WP)
Geometric mean				4.7 / 6.0						

TD = top down WS = whole system WP – water phase IS = in series with parent SP = sediment phase

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite X11449757	Distribution (max in water 44.4 – 48.3% after 5 - 22 d. Max. sed 36.9 – 50.6% after 30 - 43 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DisT ₅₀ - DisT ₉₀ whole sys.	St. (χ^2)	DisT ₅₀ - DisT ₉₀ water	χ^2	DisT ₅₀ - DisT ₉₀ sed	St. (χ^2)	Method of calculatio n
Swiss Lake	7.0	5.8	20	38 / 125	12 .1	22 / 73 days	8. 4	35 / 115 days	13 .1	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	87 / 289 days	3. 1	23 / 76 days	13 .3	114 / 378 days	3. 3	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Geometric mean				57.5 / 190						

TD = top down WS = whole system WP – water phase SP = sediment phase

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite X11406790	Distribution (max in water 12.8 – 16.5% after 2 - 5 d. Max. sed 7.0 – 10.6% after 2 - 5 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT ₅₀ - DT ₉₀ whole sys.	St. (χ^2)	DisT ₅₀ - DisT ₉₀ water	χ^2	DisT ₅₀ - DisT ₉₀ sed	St. (χ^2)	Method of calculatio n
Swiss Lake	7.0	5.8	20	7 / 23 days (dissipati on)	7. 4	7 / 25 days	14. 1	7 / 22 days	6. 7	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	1.5 / 5 days (degradati on)	2. 2	2 / 7 days	9. 5	3 / 9 days	3. 3	SFO IS (WS) SFO TD (WP) SFO TD (SP)
Geometric mean				3.2 / 10.7						

TD = top down WS = whole system WP – water phase IS = in series with parent SP = sediment phase

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Mineralization and non extractable residues					
Water / sediment system	pH water phase	pH sed	Mineralization x % after 103 d. (end of the study).	Non-extractable residues in sed. Max x % after n d	Non-extractable residues in sed. Max x % after 103 d (end of the study)
Swiss Lake	7.0	5.8	15.8% (phenyl label) 5.1% (pyridine label)	46.5% at 79 d (phenyl label) 72.4% at 79 d (pyridine label)	45.4% (phenyl label) 54.8% (pyridine label)
Calwich Abbey Lake	8.3	7.7	1.0% (phenyl label) 1.2% (pyridine label)	51.4% at 79 d (phenyl label) 56.6% at 79 d (pyridine label)	42.5% (phenyl label) 51.2% (pyridine label)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

Parent

Parameters used in FOCUSsw step 1 and 2

Parameters used in FOCUSsw step 3 (if performed)

GAP details

Version control no. of FOCUS calculator: v2.1

Version control no.'s of FOCUS software:
See below

Winter cereals 1x 7.82 g a.s./ha around the date of emergence

Winter cereals 1x 6.25 g a.s./ha around 1 January

Spring cereals 1 x 6.25 g a.s./ha at 7 days post emergence.

Winter cereals of 1 x 7.82 g a.s./ha around the date of emergence in the autumn followed by 6.25 g a.s./ha followed by an application at a minimum of 70 days afterwards and around the beginning of the next calendar year.

Step 1-2 used 2 x 7.82 g/ha with 70 day interval October-February

FOCUSsw Steps 3 & 4 software:

Tool	Component	Version	Date
SWASH	GUI	v.3 (= 3.1.2)	13 Oct 2009
	Database	v.1 (= 2.2)	Apr 2003
Spray Drift Calculator	Model (= Shell)	v.1	12 Apr 01
	Database	v.1	12 Apr 01
MACRO	Model	v.4 (= 4.3b)	-
	Shell	v.4 (= 4.4.2)	-
	Database	v.2 (= 4.4.2)	-
PRZM	Model	v.1 (= 3.21.b)	30 Jan 03
	Shell	v.1 (= 2.6)	10 Apr 03
	Data files	v.1 (= 2.0)	Sep 02
FOXSWA	Model	v.3 (= 2.1.3.F3)	28 Apr 2009
	Shell	v.3 (= 2.6)	20 May 2009
	Database	v.1 (= 2.2)	Apr 2003
SWAN	GUI	v. 1.1.4	27 Mar 2008

Step 1-2 input parameters

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Parameter	Value	Comments
XDE-729 methyl		
Molecular mass:	345	
Aqueous solubility (mg/L, 20°C):	1.7	Measured value (List of End Points)
Koc (mol/g)	987	Average Kfoc value (n = 7)
DT50 in soil(days):	20	Geomean (n = 8) SFO after 10mm rain from normalised field dissipation studies
DT50 in sediment/water (days)	1.8	Geomean of two water/sediment systems
DT50 in water (days)	1.8	Geomean of two whole system DT50
DT50 in sediment	1000	FOCUS recommended default

Steps 1-2 PEC_{sw} for XDE-729 methyl, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	1.197	---	0.412 (0.381)	---	0.332 (0.308)	---
1		0.992		0.346 (0.321)		0.279 (0.259)

Steps 1-2 PEC_{sd} for XDE-729 methyl, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	11.11	---	4.076 (3.773)	---	3.287 (3.048)	---
1		9.438		4.073 (3.770)		3.284 (3.044)

Parent Step 3

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Step 3 input parameters

Property	Value	Comment
<u>General</u>		
Molar Mass (g/mol):	345	List of End Points
Saturated vapour pressure (Pa at 20°C):	5.9×10^{-9}	Measured value (List of End Points)
Molar enthalpy vaporisation (J/mol):	95000	FOCUS default
Solubility in water (mg/L at 20°C):	1.67	Measured value (List of End Points)
Molar enthalpy of dissolution (J/mol):	27000	FOCUS default
Diffusion co-efficient in water (m ² /d):	4.3×10^{-5}	FOCUS default
Diffusion co-efficient in air (m ² /d):	0.43 *	FOCUS default
<u>Sorption</u>		
Koc (mol/g):	987	Average Kfoc value (n = 7)
Freundlich exponent	0.88	Average value (n = 7)
Ref. Conc. in liquid phase (g/m ³):	1	FOCUS default
<u>Uptake and Wash-Off</u>		
Plant root uptake factor:	0.5	FOCUS default for systemic substance
Wash-off factor from crop (MACRO, mm ⁻¹):	0.05	FOCUS default
(PRZM, cm ⁻¹):	0.50	FOCUS default
<u>Transformation</u>		
Half-life water (days, 20°C):	1.8	Geomean whole system value (n = 2)
Half-life soil (Parent only, days, 20°C):	20	
Half-life soil (for run with Acid, days, 20°C):	3.3	
Half-life sediment (days, 20°C):	1000	Worst case default
Half-life crop (days, 20°C):	10	FOCUS default
Activation energy (TOXSWA, J/mol):	65400	EFSA recommendation
Exponent (MACRO, K ⁻¹):	0.0948	EFSA recommendation
Q ₁₀ factor (PRZM):	2.58	EFSA recommendation
Formation fraction to XDE-729 Acid	0.45	Arithmetic mean (n = 8)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Step 3 results

FOCUS Step 3 PEC_{sw} values (µg/l) for XDE-729 methyl following autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	03-Oct-82	Drift	03-Oct-82	0.050
D1 Stream	03-Oct-82	Drift	03-Oct-82	0.044
D2 Ditch	03-Nov-86	Drift	03-Nov-86	0.050
D2 Stream	03-Nov-86	Drift	03-Nov-86	0.043
D3 Ditch	22-Nov-92	Drift	22-Nov-92	0.049
D4 Pond	28-Sep-85	Drift	28-Sep-85	0.002
D4 Stream	28-Sep-85	Drift	28-Sep-85	0.043
D5 Pond	27-Nov-78	Drift	27-Nov-78	0.002
D5 Stream	27-Nov-78	Drift	27-Nov-78	0.046
D6 Ditch	06-Dec-86	Drift	06-Dec-86	0.050
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.003
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.035
R3 Stream	05-Dec-80	Drift	05-Dec-80	0.046
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.041

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 3 PEC_{sw} values (µg/l) for XDE-729 methyl following autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop); 5m buffer zone for spray drift only

Scenario	App Date	Source	Date of Max PEC	Global Max
D1 Ditch	03-Oct-82	Drift	03-Oct-82	0.014
D1 Stream	03-Oct-82	Drift	03-Oct-82	0.016
D2 Ditch	03-Nov-86	Drift	03-Nov-86	0.014
D2 Stream	03-Nov-86	Drift	03-Nov-86	0.016
D3 Ditch	22-Nov-92	Drift	22-Nov-92	0.013
D4 Pond	28-Sep-85	Drift	28-Sep-85	0.001
D4 Stream	28-Sep-85	Drift	28-Sep-85	0.016
D5 Pond	27-Nov-78	Drift	27-Nov-78	0.001
D5 Stream	27-Nov-78	Drift	27-Nov-78	0.017
D6 Ditch	06-Dec-86	Drift	06-Dec-86	0.014
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.003
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.035
R3 Stream	05-Dec-80	Runoff	16-Dec-80	0.041
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.041

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 3 PEC_{sw} values (µg/l) for XDE-729 methyl following spring application to winter cereals at 6.25 g as/ha using field DT50 inputs (earliest application at emergence of crop); application window start 1st January

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	16-Jan-82	Drift	16-Jan-82	0.040
D1 Stream	16-Jan-82	Drift	16-Jan-82	0.035
D2 Ditch	12-Jan-86	Drift	12-Jan-86	0.039
D2 Stream	12-Jan-86	Drift	12-Jan-86	0.030
D3 Ditch	30-Jan-92	Drift	30-Jan-92	0.039
D4 Pond	16-Jan-85	Drift	16-Jan-85	0.001
D4 Stream	16-Jan-85	Drift	16-Jan-85	0.031
D5 Pond	02-Jan-78	Drift	02-Jan-78	0.001
D5 Stream	02-Jan-78	Drift	02-Jan-78	0.029
D6 Ditch	14-Jan-86	Drift	14-Jan-86	0.040
R1 Pond	01-Jan-79	Drift	01-Jan-79	0.001
R1 Stream	01-Jan-79	Drift	01-Jan-79	0.026
R3 Stream	19-Feb-81	Drift	19-Feb-81	0.037
R4 Stream	04-Jan-80	Drift	04-Jan-80	0.026

FOCUS Step 3 PEC_{sw} values (µg/l) for XDE-729 methyl following a double application of XDE-729 methyl to winter cereals in autumn at 7.82 g/ha followed by spring application at 6.25 g as/ha using field DT50 inputs; run-off scenarios only

Scenario	App Dates (Aut+Spring)	Source	Date of Max PEC	Global Max.
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.003
R1 Stream	24-Feb-79	Runoff	25-Nov-78	0.035
R3 Stream	06-Dec-80 19-Feb-81	Runoff	16-Dec-80	0.041
R4 Stream	10-Nov-79 21-Jan-80	Runoff	21-Dec-79	0.041

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 3 PEC_{sw} values (µg/l) for XDE-729 methyl following spring application to spring cereals at 6.25 g as/ha using field DT50 inputs (earliest application 7 days post emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max
D1 Ditch	14-May-82	Drift	14-May-82	0.039
D1 Stream	14-May-82	Drift	14-May-82	0.031
D3 Ditch	07-Apr-92	Drift	07-Apr-92	0.039
D4 Pond	30-May-85	Drift	30-May-85	0.001
D4 Stream	30-May-85	Drift	30-May-85	0.033
D5 Pond	08-Apr-78	Drift	08-Apr-78	0.001
D5 Stream	08-Apr-78	Drift	08-Apr-78	0.031
R4 Stream	22-Mar-84	Drift	22-Mar-84	0.026

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Step 4 results

FOCUS Step 4 PEC_{sw} values (µg/l) for XDE-729 methyl following autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop); 10 and 20 m buffer zone for spray drift and run-off

Scenario	App Date	Source	Date of Max PEC	Global Max.
10m Drift + Runoff				
D1 Ditch	03-Oct-82	Drift	03-Oct-82	0.007
D1 Stream	03-Oct-82	Drift	03-Oct-82	0.008
D2 Ditch	03-Nov-86	Drift	03-Nov-86	0.007
D2 Stream	03-Nov-86	Drift	03-Nov-86	0.008
D3 Ditch	22-Nov-92	Drift	22-Nov-92	0.007
D4 Pond	28-Sep-85	Drift	28-Sep-85	0.001
D4 Stream	28-Sep-85	Drift	28-Sep-85	0.008
D5 Pond	27-Nov-78	Drift	27-Nov-78	0.001
D5 Stream	27-Nov-78	Drift	27-Nov-78	0.009
D6 Ditch	06-Dec-86	Drainflow	19-Jan-87	0.009
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.001
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.016
R3 Stream	05-Dec-80	Runoff	16-Dec-80	0.019
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.018
20m Drift + Runoff				
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.001
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.008
R3 Stream	05-Dec-80	Runoff	16-Dec-80	0.010
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.010

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 4 PEC_{sw} values (µg/l) for XDE-729 methyl following spring application to winter cereals at 6.25 g as/ha using field DT50 inputs (earliest application at emergence of crop); application window start 1st January. 5m buffer (spray drift only) and 10 m buffer zone (spray drift and run-off)

Scenario	App Date	Source	Date of Max PEC	Global Max.
5 m Drift Only				
D1 Ditch	16-Jan-82	Drift	16-Jan-82	0.011
D1 Stream	16-Jan-82	Drift	16-Jan-82	0.013
D2 Ditch	12-Jan-86	Drift	12-Jan-86	0.011
D2 Stream	12-Jan-86	Drift	12-Jan-86	0.011
D3 Ditch	30-Jan-92	Drift	30-Jan-92	0.010
D4 Pond	16-Jan-85	Drift	16-Jan-85	0.001
D4 Stream	16-Jan-85	Drift	16-Jan-85	0.011
D5 Pond	02-Jan-78	Drift	02-Jan-78	0.001
D5 Stream	02-Jan-78	Drift	02-Jan-78	0.010
D6 Ditch	14-Jan-86	Drift	14-Jan-86	0.011
R1 Pond	01-Jan-79	Drift	01-Jan-79	0.001
R1 Stream	01-Jan-79	Runoff	02-Feb-79	0.020
R3 Stream	19-Feb-81	Runoff	03-Mar-81	0.018
R4 Stream	04-Jan-80	Runoff	19-Mar-80	0.016
10 m Drift + Runoff Reduction				
R1 Pond	01-Jan-79	Drift	01-Jan-79	0.001
R1 Stream	01-Jan-79	Runoff	02-Feb-79	0.009
R3 Stream	19-Feb-81	Runoff	03-Mar-81	0.008
R4 Stream	04-Jan-80	Runoff	19-Mar-80	0.007

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 4 PEC_{sw} values (µg/l) for XDE-729 methyl following spring application to spring cereals at 6.25 g as/ha using field DT50 inputs (earliest application 7 days post emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max
Step 4 – 5m Drift Only				
D1 Ditch	14-May-82	Drift	14-May-82	0.011
D1 Stream	14-May-82	Drift	14-May-82	0.011
D3 Ditch	07-Apr-92	Drift	07-Apr-92	0.011
D4 Pond	30-May-85	Drift	30-May-85	0.001
D4 Stream	30-May-85	Drift	30-May-85	0.012
D5 Pond	08-Apr-78	Drift	08-Apr-78	0.001
D5 Stream	08-Apr-78	Drift	08-Apr-78	0.011
R4 Stream	22-Mar-84	Drift	22-Mar-84	0.018
Step 4 – 10m Drift + Runoff				
R4 Stream	22-Mar-84	Runoff	15-May-84	0.008

Metabolite X11393729

Step 1-2 input parameters

X11393729		
Molar mass	331	
Aqueous solubility (mg/L, 20°C):	3070	Measured value (List of End Points)
Maximum observed in water/sediment	23.5%	
Maximum observed in soil	40.1%	From field studies
Koc	28	Average K _{foc} from the highest pH soils
DT50 soil (days)	72.6	Geomean normalised DT50 from two alkaline field soils
DT50 in sediment/water (days)	4.7	Geomean of two water/sediment systems
DT50 in water (days)	4.7	Geomean whole system of two water/sediment systems
DT50 in sediment	1000	FOCUS recommended default

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Steps 1-2 PEC_{sw} for X11393729, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.983	---	0.536 (0.358)	---	0.430 (0.288)	---
1		0.915		0.499 (0.333)		0.401 (0.268)

Steps 1-2 PEC_{sd} for X11393729, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.271	---	0.150 (0.100)	---	0.120 (0.081)	---
1		0.254		0.140 (0.094)		0.112 (0.075)

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Step 3 & 4 input parameters

Property	Value	Comment
<u>General</u>		
Molar Mass (g/mol):	331	List of End Points
Sat. vapour pressure (Pa at 20°C):	2.0×10^{-5}	Measured value (List of End Points)
Molar enthalpy vaporisation (J/mol):	95000	FOCUS default
Solubility in water (mg/L at 20°C):	3070	Measured value at pH 7 (List of End Points)
Molar enthalpy of dissolution (J/mol):	27000	FOCUS default
Diffusion co-efficient in water (m ² /d):	4.3×10^{-5}	FOCUS default
Diffusion co-efficient in air (m ² /d):	0.43	FOCUS default
<u>Sorption (average inputs)</u>		
K _{oc} (mol/g):	27.5	Average K _{oc} from the highest pH soils (n = 2)
Freundlich exponent	0.88	Average 1/n from the highest pH soils (n = 2)
Ref. Conc. in liquid phase (g/m ³):	1	FOCUS default
<u>Uptake and Wash-Off</u>		
Plant root uptake factor:	0	No data. Default worst case
Wash-off factor from crop (MACRO, mm ⁻¹):	0.05	FOCUS default
(PRZM, cm ⁻¹):	0.50	FOCUS default
<u>Transformation</u>		
Half-life water (days, 20°C):	4.7	Geomean whole system value (n = 2)
Half-life soil (days, 20°C):	22	Geomean from field sites, normalised (n = 8)
Formation fraction in soil:	0.45	Average from field sites, normalised (n = 8)
Half-life sediment (days, 20°C):	1000	Worst case default
Half-life crop (days, 20°C):	10	FOCUS default
Act. energy (TOXSWA, J/mol):	65400	EFSA recommendation
Exponent (MACRO, K ⁻¹):	0.0948	EFSA recommendation
Q ₁₀ factor (PRZM):	2.58	EFSA recommendation

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Step 3 results

FOCUS Step 3 PEC_{sw} values (µg/l) for X11393729 following XDE-729 methyl autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	03-Oct-82	Drainflow	25-Nov-82	0.217
D1 Stream	03-Oct-82	Drainflow	24-Nov-82	0.136
D2 Ditch	03-Nov-86	Drainflow	20-Nov-86	0.293
D2 Stream	03-Nov-86	Drainflow	20-Nov-86	0.184
D3 Ditch	22-Nov-92	Drainflow	09-Feb-93	0.000
D4 Pond	28-Sep-85	Drainflow	23-Dec-85	0.024
D4 Stream	28-Sep-85	Drainflow	07-Dec-85	0.043
D5 Pond	27-Nov-78	Drainflow	13-Feb-79	0.028
D5 Stream	27-Nov-78	Drainflow	24-Jan-78	0.045
D6 Ditch	06-Dec-86	Drainflow	18-Dec-86	0.112
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.001
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.059
R3 Stream	05-Dec-80	Runoff	16-Dec-80	0.061
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.032

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 3 PEC_{sw} values (µg/l) for X11393729 following XDE-729 methyl spring application to winter cereals at 6.25 g as/ha using field DT50 inputs (earliest application on 1st January)

Scenario	App Date	Source	Date of Max PEC	Global Max
D1 Ditch	16-Jan-82	Drainflow	10-Apr-82	0.109
D1 Stream	16-Jan-82	Drainflow	10-Apr-82	0.068
D2 Ditch	12-Jan-86	Drainflow	27-Mar-86	0.212
D2 Stream	12-Jan-86	Drainflow	27-Mar-86	0.132
D3 Ditch	30-Jan-92	Drainflow	25-Apr-92	0.000
D4 Pond	16-Jan-85	Drainflow	24-Dec-85	0.001
D4 Stream	16-Jan-85	Drainflow	02-Feb-85	0.002
D5 Pond	02-Jan-78	Drainflow	29-Jan-78	0.024
D5 Stream	02-Jan-78	Drainflow	24-Jan-78	0.055
D6 Ditch	14-Jan-86	Drainflow	09-Feb-86	0.097
R1 Pond	01-Jan-79	Runoff	02-Feb-79	0.001
R1 Stream	01-Jan-79	Runoff	02-Feb-79	0.018
R3 Stream	19-Feb-81	Runoff	03-Mar-81	0.019
R4 Stream	04-Jan-80	Runoff	19-Mar-80	0.006

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 3 PEC_{sw} values (µg/l) for X11393729 following a double application of XDE-729 methyl to winter cereals in autumn at 7.82 g/ha followed by spring application at 6.25 g as/ha using field DT50 inputs

App Dates*	Scenario	Source	Date of Max PEC	Global Max
29-Sep-81 16-Jan-82 03-Oct-82	D1 Ditch D1 Stream	Drainflo w Drainflo w	24-Nov-82 24-Nov-82	0.210 0.132
30-Oct-85 12-Jan-86 03-Nov-86	D2 Ditch D2 Stream	Drainflo w Drainflo w	20-Nov-86 20-Nov-86	0.281 0.176
27-Nov-91 07-Feb-92 22-Nov-92	D3 Ditch	Drainflo w	09-Feb-93	0.000
29-Sep-84 16-Jan-85 28-Sep-85	D4 Pond D4 Stream	Drainflo w Drainflo w	23-Dec-85 07-Dec-85	0.024 0.042
02-Dec-77 10-Feb-78 27-Nov-78	D5 Pond D5 Stream	Drainflo w Drainflo w	13-Feb-79 24-Jan-78	0.027 0.044
16-Dec-85 27-Feb-86 06-Dec-86	D6 Ditch	Drainflo w	18-Dec-86	0.103
14-Nov-78 24-Feb-79	R1 Pond R1 Stream	Runoff Runoff	31-Dec-78 25-Nov-78	0.001 0.059
06-Dec-80 19-Feb-81	R3 Stream	Runoff	16-Dec-80	0.061
10-Nov-79 21-Jan-80	R4 Stream	Runoff	21-Dec-79	0.032

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS Step 3 PEC_{sw} values (µg/l) for X11393729 following XDE-729 methyl spring application to spring cereals at 6.25 g as/ha using field DT50 inputs (earliest application 7 days post emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	14-May-82	Drainflow	22-Sep-82	0.015
D1 Stream	14-May-82	Drainflow	21-Sep-82	0.017
D3 Ditch	07-Apr-92	Drainflow	10-Feb-93	0.000
D4 Pond	30-May-85	Drainflow	23-Dec-85	0.001
D4 Stream	30-May-85	Drainflow	09-Dec-85	0.001
D5 Pond	08-Apr-78	Drainflow	31-Jan-78	0.000
D5 Stream	08-Apr-78	Drainflow	03-Jan-78	0.000
R4 Stream	22-Mar-84	Runoff	15-May-84	0.027

Step 4 results

FOCUS Step 4 PEC_{sw} values (µg/l) for X11393729 following XDE-729 methyl autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
Step 4 (10m Drift and Runoff)				
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.000
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.027
R3 Stream	05-Dec-80	Runoff	16-Dec-80	0.028
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.014

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite X11449757

Steps 1-2 input parameters

X11449757		
Molar mass	317	
Aqueous solubility (mg/L, 20°C):	265	Measured value (List of End Points)
Maximum observed in water/sediment	76.7%	
Maximum observed in soil	13.8%	From laboratory studies
Koc	17	Average Kfoc from the highest pH soils
DT50 soil (days)	67	Geomean of field normalised top-down SFO DT50
DT50 in sediment/water (days)	57.5	Geomean of two water/sediment systems
DT50 in water (days)	57.5	Geomean whole system of two water/sediment systems
DT50 in sediment	1000	FOCUS recommended default

Steps 1-2 results

Steps 1-2 PEC_{sw} for X11449757, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.748		0.233 (0.164)		0.198 (0.141)	
1		0.742		0.231 (0.163)		0.197 (0.140)

Steps 1-2 PEC_{sd} for X11449757, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.252		0.040 (0.028)		0.034 (0.024)	
1		0.122 (day 4)		0.039 (0.028)		0.033 (0.024)

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Metabolite X11406790

Steps 1-2 input parameters

X11406790		
Molar mass	331	
Aqueous solubility (mg/L, 20°C):	3070	Taken as identical to X11393729 in absence of data
Maximum observed in water/sediment	23.6%	
Maximum observed in soil	1.4%	From laboratory studies
Koc	0/1000*	Default, no data available
DT50 soil (days)	1000	Worst case default, no data available
DT50 in sediment/water (days)	3.2	Geomean of two water/sediment systems
DT50 in water (days)	3.2	Geomean whole system of two water/sediment systems
DT50 in sediment	1000	FOCUS recommended default

*In absence of data, “worst” and “best” cases used as Koc determines partitioning into sediment at Step 1-2

Step 1-2 results

Steps 1-2 PEC_{sw} for X11406790, two applications to winter cereals (values in brackets are from single application) assuming Koc = 0

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.051		0.032 (0.020)		0.026 (0.017)	
1		0.046		0.028 (0.018)		0.024 (0.016)

Steps 1-2 PEC_{sed} for X11406790, two applications to winter cereals (values in brackets are from single application) assuming Koc = 0

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.000		0.000 (0.000)		0.000 (0.000)	
1		0.000		0.000 (0.000)		0.000 (0.000)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Steps 1-2 PEC_{sw} for X11406790, two applications to winter cereals (values in brackets are from single application) assuming K_{oc} = 1000

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.031		0.015 (0.016)		0.014 (0.016)	
1		0.024		0.014 (0.012)		0.010 (0.012)

Steps 1-2 PEC_{sd} for X11406790, two applications to winter cereals (values in brackets are from single application) assuming K_{oc} = 1000

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.177 (day 1)		0.149 (0.100)		0.127 (0.089)	
1		0.164		0.142 (0.096)		0.122 (0.085)

Aqueous photolysis metabolites of XDE-729 methyl

PEC_{sw} values for aqueous photolysis metabolites of XDE-729 methyl

Photoproduct	Molecular weight	Max % in water	Step 1	Step 2 North Oct-Feb	Step 2 South Oct-Feb
XDE-729 methyl	345	-	1.197	0.412	0.332
Deg 10	326	12.6	0.234	0.049	0.039
Deg 11	273	15.7	0.178	0.061	0.049
Deg 14	229	11.5	0.091	0.031	0.025

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study
(e.g. modelling, field leaching, lysimeter)

For FOCUS gw modelling, values used –
Modelling using FOCUS models, with appropriate FOCUSgw scenarios, according to FOCUS guidance.
Model(s) used: FOCUS PELMO 4.4.3 & FOCUS PEARL 4.4.4
Scenarios (list of names): See below
Crop: Winter and spring cereals
See below for GAP and input parameters.

Application rate

Winter cereals in the autumn at 7.82 g as/ha at crop growth stage BBCH 10-29 (25% interception, applied dose 5.865 g/ha) followed by a second application in the spring at 6.25 g as/ha at growth stage BBCH 13-45 (25% interception, dose applied 4.688 g/ha) with a minimum 70 day interval. First application set to date of emergence, second application set to 70 days after emergence.

Winter cereals in the autumn at 7.82 g as/ha at crop growth stage BBCH 10-29 (25% interception, applied dose 5.865 g/ha). Application set to date of emergence.

Winter cereals in the spring at 6.25 g as/ha at growth stage BBCH 13-45 (25% interception, dose applied 4.688 g/ha). Application set to 1st January.

Spring cereals in the spring at 6.25 g as/ha at growth stage BBCH 13-45 (25% interception, dose applied 4.688 g/ha). Application set to 7 days post-emergence.

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Substance input parameters:

FOCUS PELMO inputs for XDE-729 methyl (simulating parent only)

Parameter	Value	Comments
Molecular mass:	345	
Plant uptake factor:	0.5	FOCUS recommendation for systemic substance
<u>Volatilisation and photolysis data</u>		
Vapour pressure (Pa, 20°C):	5.9×10^{-9}	Measured value (List of End Points)
Aqueous solubility (mg/L, 20°C):	1.7	Measured value (List of End Points)
Soil photolysis rate (d^{-1}):	0	Photolysis not considered
Diffusion coeff. air (cm^2/s):	0.05	FOCUS recommendation
Volatilisation depth (cm):	0.1	FOCUS recommendation
<u>Sorption data</u>		
Koc (mol/g)	987	Average Kfoc value (n = 7)
Freundlich exponent (1/n)	0.88	Average value (n = 7)
pKa	20	Default to disable pH dependence
Increase for air-dried soil:	1	FOCUS recommendation
Kinetic sorption parameters:	0	Kinetic sorption not implemented
Depth dependent data	Standard (Tier 1)	FOCUS recommendation
<u>Degradation data:</u>		
DT50 (days, 20°C, pF2):	20	Geomean (n = 8) SFO after 10mm rain from normalised field dissipation studies
Rate correction in soil option:	Recommended	FOCUS recommendation
Rel. deg at neq sites:	0	FOCUS recommendation

Note: FOCUS default values were used for any other input parameters not shown

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS PEARL inputs for XDE-729 methyl (simulating parent only)

Parameter	Value	Comments
<u>General data</u>		
Molar mass (g/mole):	345	-
Sat. vap. pressure (Pa, 20°C):	5.9×10^{-9}	Measured value (List of End Points)
Sol in water (mg/L, 20°C):	1.7	Measured value (List of End Points)
Enthalpy of vaporisation (kJ/mole):	95	FOCUS recommendation
Enthalpy of dissolution (kJ/mole):	27	FOCUS recommendation
<u>Sorption data</u>		
Option:	Kom, pH independent	
Kom, (mol/g at 20 °C) [†] :	573	Average Kfom value (n= 7)
Enthalpy of sorption (kJ/mole):	0	Not implemented
Equilibrium sorption:		
Ref. conc. in liq. phase (mg/L):	1	FOCUS recommendation
Freundlich exponent (1/n):	0.88	Average value (n = 7)
Non-equilibrium sorption:		
Desorption rate coeff. (d ⁻¹):	0	Non-equilibrium sorption not implemented
Factor Kf,neq/Kf,eq:	0	Non-equilibrium sorption not implemented
<u>Transformation data</u>		
Half-life (days at 20°C):	20	Geomean (n = 8) SFO after 10mmm rain from normalised field dissipation studies
Optimum moisture conditions	Yes	Relevant for pF 2
Exponent for effect of liquid:	0.7	FOCUS recommendation
Molar act. energy (kJ/mole):	65.4	EFSA recommendation
<u>Diffusion data</u>		
Ref temperature (°C):	20	FOCUS recommendation
Ref diff. coeff. in water (m ² /d):	4.3×10^{-5}	FOCUS recommendation
Ref diff. coeff. in air (m ² /d) :	0.43	FOCUS recommendation
<u>Crop data</u>		
Wash-off factor (m ⁻¹):	0.0001	FOCUS recommendation
Canopy process option:	Lumped	FOCUS recommendation
Half-life at crop surface (d):	1000000	FOCUS recommendation
Coeff. for uptake by plant	0.5	FOCUS recommendation for systemic substance

[†] Kom = Koc/1.724

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS PELMO and PEARL Inputs for X11393729 (formed from parent)

Parameter	Value	Comments
<u>General data</u>		
Molecular mass:	331	-
Plant uptake factor:	0	Worst-case value
Sat. vap. pressure (Pa, 20°C):	2×10^{-5}	Measured value
Sol in water (mg/L, 20°C):	3070	Measured value at pH 7
<u>Sorption data</u>		
K _{foc} (mol/g):	28	Average K _{foc} from the highest pH soils (n = 2)
K _{fom} (mol/g):	16.0	From K _{foc} /1.724
Freundlich exponent:	0.88	Average 1/n from the highest pH soils (n = 2)
<u>Transformation data</u>		
DT50 Parent (days, 20°C/pF2):	3.3	From sequential modelling of parent and X11393729, normalised field data
Rate constant, k (d ⁻¹):	0.210	From $\ln 2 / DT50$
DT50 Acid (days, 20°C/pF2):	22	From sequential modelling of parent + X11393729, normalised field data
Formation fraction:	0.45	From sequential modelling of parent + X11393729, normalised field data
Rate constant, k (d ⁻¹):		
Parent > Acid (d ⁻¹)	0.0945	Based on FF = 0.45
Parent > CO ₂ /NER (d ⁻¹)	0.1155	Based on FF = (1 – 0.45)

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

FOCUS PELMO and PEARL Inputs for X11449757 (formed in sequence from parent and X11393729)

Parameter	Value	Comments
<u>General data</u>		
Molecular mass:	317	-
Plant uptake factor:	0	Worst-case value
Sat. vap. pressure (Pa, 20°C):	5×10^{-5}	Measured value (List of End Points)
Sol in water (mg/L, 20°C):	265	Measured value at pH 7 (List of End Points)
<u>Sorption data</u>		
Kfoc (mol/g):	17	Average Kfoc from the highest pH soils (n = 2)
Kfom (mol/g):	9.9	From Kfoc/1.724
Freundlich exponent:	0.93	Average Kfoc from the highest pH soils (n = 2)
<u>Transformation data</u>		
DT50 Parent (days, 20°C/pF2):	1.7	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Rate constant, k (d ⁻¹):	0.408	From ln2/DT50
Parent > Acid (d ⁻¹):	0.2162	Based on FF = 0.53
Parent > CO ₂ /NER (d ⁻¹):	0.1918	Based on FF = (1 – 0.53)
DT50 Acid (days, 20°C/pF2):	14	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Formation fraction (from parent):	0.53	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Rate constant, k total (d ⁻¹):	0.0495	From ln2/DT50
Acid > X-757 (d ⁻¹):	0.0297	Based on FF = 0.60
Acid > CO ₂ /NER (d ⁻¹):	0.0198	Based on FF = (1 – 0.60)
DT50 X-757 (days, 20°C/pF2):	19	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Formation fraction (from X11393729):	0.60	From sequential modelling of parent + X11393729 + X11449757, normalised field data

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m)

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

80th percentile PECgw Values (µg/l) for XDE-729 methyl following application to winter cereals

Scenario	Crop emerg. date (dd/mm)	Autumn, 7.82 g/ha at emergence, 25% int		Spring, 6.25 g/ha on 1 st Jan, 25% int		*Double app, autumn + spring with 70 d interval	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	26/10	0.000	0.000	0.000	0.000	0.000	0.000
Hamburg	01/11	0.000	0.000	0.000	0.000	0.000	0.000
Jokioinen	20/09	0.000	0.000	0.000	0.000	0.000	0.000
Kremsmünster	05/11	0.000	0.000	0.000	0.000	0.000	0.000
Okehampton	17/10	0.000	0.000	0.000	0.000	0.000	0.000
Piacenza	01/12	0.000	0.000	0.000	0.000	0.000	0.000
Porto	30/11	0.000	0.000	0.000	0.000	0.000	0.000
Sevilla	30/11	0.000	0.000	0.000	0.000	0.000	0.000
Thiva	30/11	0.000	0.000	0.000	0.000	0.000	0.000

* Application scheme is 7.82 g as/ha at emergence with 25% intercept (5.865 g/ha to soil) followed by 6.25 g as/ha at 70 days post-emergence with 25% intercept (4.688 g/ha to soil)

80th percentile PECgw values (µg/l) for X11393729 following application of XDE-729 methyl to winter cereals

Scenario	Crop emerg. date (dd/mm)	Autumn, 7.82 g/ha at emergence, 25% int		Spring, 6.25 g/ha on 1 st Jan, 25% int		*Double app, autumn + spring with 70 d interval	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	26/10	0.001	0.001	0.000	0.000	0.001	0.001
Hamburg	01/11	0.010	0.008	0.003	0.002	0.016	0.012
Jokioinen	20/09	0.003	0.002	0.001	0.000	0.005	0.004
Kremsmünster	05/11	0.004	0.003	0.002	0.001	0.007	0.006
Okehampton	17/10	0.012	0.011	0.005	0.003	0.019	0.015
Piacenza	01/12	0.005	0.003	0.002	0.002	0.008	0.006
Porto	30/11	0.010	0.006	0.006	0.002	0.012	0.007
Sevilla	30/11	0.000	0.000	0.000	0.000	0.000	0.000
Thiva	30/11	0.000	0.000	0.000	0.000	0.000	0.000

* Application scheme is 7.82 g as/ha at emergence with 25% intercept (5.865 g/ha to soil) followed by 6.25 g as/ha at 70 days post-emergence with 25% intercept (4.688 g/ha to soil)

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

80th percentile PEC_{gw} values (µg/l) for X11449757 following application of XDE-729 methyl to winter cereals

Scenario	Crop emerg. date (dd/mm)	Autumn, 7.82 g/ha at emergence, 25% int		Spring, 6.25 g/ha on 1 st Jan, 25% int		*Double app, autumn + spring with 70 d interval	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	26/10	0.007	0.009	0.003	0.004	0.011	0.016
Hamburg	01/11	0.048	0.040	0.019	0.017	0.068	0.059
Jokioinen	20/09	0.037	0.027	0.013	0.010	0.053	0.042
Kremsmünster	05/11	0.024	0.019	0.013	0.010	0.040	0.032
Okehampton	17/10	0.049	0.043	0.020	0.017	0.073	0.059
Piacenza	01/12	0.018	0.013	0.008	0.009	0.024	0.023
Porto	30/11	0.041	0.029	0.016	0.010	0.047	0.034
Sevilla	30/11	0.001	0.000	0.000	0.000	0.001	0.000
Thiva	30/11	0.003	0.002	0.001	0.001	0.003	0.004

* Application scheme is 7.82 g as/ha at emergence with 25% intercept (5.865 g/ha to soil) followed by 6.25 g as/ha at 70 days post-emergence with 25% intercept (4.688 g/ha to soil)

80th percentile PEC_{gw} values (µg/l) for XDE-729 methyl and metabolites (XDE-729 Acid = X11393729, X-757 = X11449757) following a single application to spring cereals

Scenario	Application Date (dd/mm)	XDE-729 methyl		XDE-729 Acid		X-757	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	17/03	0.000	0.000	0.000	0.000	0.001	0.002
Hamburg	08/04	0.000	0.000	0.001	0.002	0.013	0.019
Jokioinen	25/05	0.000	0.000	0.001	0.000	0.015	0.013
Kremsmünster	08/04	0.000	0.000	0.001	0.001	0.011	0.011
Okehampton	08/04	0.000	0.000	0.002	0.002	0.014	0.014
Porto	17/03	0.000	0.000	0.001	0.000	0.006	0.003

Application scheme is one application of 6.25 g as/ha at 7 days post-emergence with 25% intercept (4.688 g/ha to soil)

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	active substance: 5.6
Photochemical oxidative degradation in air ‡	DT ₅₀ of 2.2 days derived by the Atkinson model (AopWin version 1.92). OH (12 h) concentration assumed = 1.5×10^6 radicals/cm ³
Volatilisation ‡	Not submitted, not required
Metabolites	X11393729 unlikely to be volatile

PEC (air)

Method of calculation	Expert judgement, based on vapour pressure, dimensionless Henry's Law Constant and information on volatilisation from plants and soil.
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PEC_(a)

Maximum concentration	Expected to be negligible
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‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Fate and behaviour in the environment

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).

Soil:	parent XDE-729 methyl, X11393729 and X11449757
Surface Water:	parent XDE-729 methyl, X11393729, X11406790, X11449757, and aqueous photolysis metabolites Deg 10, Deg11 and Deg 14
Sediment:	parent XDE-729 methyl, X11393729, X11406790 and X11449757, and aqueous photolysis metabolites Deg 10, Deg11 and Deg 14
Ground water:	parent XDE-729 methyl, X11393729 and X11449757
Air:	parent XDE-729 methyl

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	New active substance; not submitted, not required
Surface water (indicate location and type of study)	New active substance; not submitted, not required
Ground water (indicate location and type of study)	New active substance; not submitted, not required
Air (indicate location and type of study)	New active substance; not submitted, not required

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

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List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Species	Test substance	Time scale	End point	End point
Birds ‡				
Bobwhite quail	a.s.	Acute	LD ₅₀ >2250 mg/kg bw	-
Zebra finch	a.s.	Acute	LD ₅₀ >2250 mg/kg bw	-
Bobwhite quail	GF-2573	Acute	LD ₅₀ >2000 mg/kg bw ¹	-
Bobwhite quail	a.s.	Short-term	ED ₅₀ >1328 mg/kg bw/day	LC ₅₀ >5260 mg/kg feed
Mallard duck	a.s.	Short-term	LD ₅₀ >2088 mg/kg bw/day	LC ₅₀ >5260 mg/kg feed
Bobwhite quail	a.s.	Reproduction	NOAEL = 36.9 mg/kg bw/day	NOEC = 400 mg/kg feed
Mallard duck	a.s.	Reproduction	NOAEL = 160.5 mg/kg bw/day	NOEC = 1000 mg/kg feed
Mammals ‡				
Rat	a.s.	Acute	LD ₅₀ >5000 mg/kg bw	-
Rat	GF-2573	Acute	LD ₅₀ >5000 mg/kg bw ¹	-
Rabbit	a.s.	Long-term	NOAEL = 5.78 mg/kg bw/day ²	-

¹ mg formulation/kg b.w.

² The endpoint stated for reproductive toxicity has only been used in the screening step of the assessment. This endpoint was used in the human risk assessment to set the ADI. Therefore it is a more conservative approach which is not a true reflection of reproductive toxicity, had the TER at screening step fallen below the trigger value of 5 then this endpoint would have been refined at tier 1.

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Cereals 1 x 0.00782 kg a.s./ha

Indicator species	Time scale	DDD	TER ¹	Annex VI Trigger ³
Screening step (Birds)				
Small omnivorous bird	Acute (a.s)	1.24	3421	10
Small omnivorous bird	Acute (GF-2573)	144	22.41	10
Small omnivorous bird	Long-term (a.s)	0.27	137	5

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Indicator species	Time scale	DDD	TER ¹	Annex VI Trigger
Screening step (Mammals)				
Small herbivorous mammal	Acute (a.s)	0.93	>5400	10
Small herbivorous mammal	Acute (GF-2573)	107.4	46.56	10
Small herbivorous mammal	Long-term (a.s)	0.20	28.87	5

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	End point	Toxicity ¹ (mg/L)
Laboratory tests ‡				
Fish				
Sheepshead minnow (<i>Cyprinodon variegates</i>)	a.s.	96 hr	LC ₅₀	> 1.33 (mm)
Sheepshead minnow (<i>Cyprinodon variegates</i>)	a.s.	28 d	NOEC	0.0115 (mm)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	GF-2573	96 hr	LC ₅₀	78.7 (nom)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	XDE-729 acid (X11393729)	96 hr	LC ₅₀	>107 (mm)
Fathead minnow (<i>Pimephales promelas</i>)	XDE-729 acid	28 d	NOEC	11.8 (mm)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	X11449757	96 hr	LC ₅₀	>120 (nom)
Fathead minnow (<i>Pimephales promelas</i>)	X11449757	28 d	NOEC	8.9 (mm)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Group	Test substance	Time-scale (Test type)	End point	Toxicity ¹ (mg/L)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	X11406790	96 hr	LC ₅₀	>30 (nom)
Fathead minnow (<i>Pimephales promelas</i>)	a.s.	21-day reproduction assay	NOEC	0.078 (mm)
Fathead minnow (<i>Pimephales promelas</i>)	XDE-729 acid	21-day reproduction assay	NOEC	12 (mm)
Aquatic invertebrate				
Water flea (<i>Daphnia magna</i>)	a.s.	48 hr	EC ₅₀	2.12 (mm)
Mysid Shrimp (<i>Americamysis bahia</i>)	a.s.	96 hr	LC ₅₀	>1.30 (mm)
Eastern Oyster (<i>Crassostrea virginica</i>)	a.s.	96 hr	EC ₅₀	>1.21 (mm)
Water flea (<i>Daphnia magna</i>)	a.s.	21 d	NOEC	0.144 (mm)
Mysid Shrimp (<i>Americamysis bahia</i>)	a.s.	28 d	NOEC	0.152 (mm)
Marine Amphipod (<i>Leptocheirus Plumulosus</i>)	a.s.	10 d	LC ₅₀	>58.1 mg/kg (sediment treated)
Water flea (<i>Daphnia magna</i>)	GF-2573	48 hr	EC ₅₀	14.0 (nom)
Water flea (<i>Daphnia magna</i>)	GF-2573 (blank formulation)*	48 hr	EC ₅₀	9.1 (nom)
Water flea (<i>Daphnia magna</i>)	XDE-729 acid	48 hr	EC ₅₀	>106 (mm)
Water flea (<i>Daphnia magna</i>)	XDE-729 acid	21 d	NOEC	100 (nom)
Water flea (<i>Daphnia magna</i>)	X11449757	48 hr	EC ₅₀	>120 (nom)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Group	Test substance	Time-scale (Test type)	End point	Toxicity ¹ (mg/L)
Water flea (<i>Daphnia magna</i>)	X11406790	48 hr	EC ₅₀	>30 (nom)
Sediment dwelling organisms				
Freshwater midge (<i>Chironomus riparius</i>)	a.s.	28 d	NOEC	1.26 (im)
Freshwater midge (<i>Chironomus dilutes</i>)	a.s.	28 d	NOEC	89.3 mg/kg (sediment treated)
Algae				
<i>Pseudokirchneriella subcapitata</i>	a.s.	72 hr / 96 hr	72 hr E _y C ₅₀ / E _r C ₅₀ 96 hr E _y C ₅₀ / E _r C ₅₀	>0.855 (mm) >0.245 (mm)
<i>Pseudokirchneriella subcapitata</i>	GF-2573	72 hr	E _y C ₅₀ E _r C ₅₀	0.29 (nom) 1.1 (nom)
<i>Pseudokirchneriella subcapitata</i>	██████ (co-formulant of GF-2573)	72 hr	E _y C ₅₀ E _r C ₅₀	0.37 (nom) 2.9 (nom)
<i>Pseudokirchneriella subcapitata</i>	XDE-729 acid	72 hr	E _y C ₅₀ E _r C ₅₀	23 (nom) 63 (nom)
<i>Pseudokirchneriella subcapitata</i>	X11449757	72 hr	E _y C ₅₀ E _r C ₅₀	4.13 (mm) >15.8 (mm)
<i>Pseudokirchneriella subcapitata</i>	X11406790	72 hr	E _y C ₅₀ E _r C ₅₀	1.8 (mm) >5.7 (mm)
Higher plant				
Duckweed (<i>Lemna gibba</i>)	a.s.	7 d	E _y C ₅₀ E _r C ₅₀	2.13 (mm) >2.27 (mm)
Eurasian watermilfoil (<i>Myriophyllum spicatum</i>)	a.s.	14 d	E _y C ₅₀ E _r C ₅₀	0.000149 (nom) 0.000393 (nom)
Duckweed (<i>Lemna gibba</i>)	GF-2573	7 d	E _y C ₅₀ E _r C ₅₀	>80 (mm) >80 (mm)
Eurasian watermilfoil (<i>Myriophyllum spicatum</i>)	GF-2573	14 d	E _y C ₅₀ E _r C ₅₀	0.0402 (nom) 0.0844 (nom)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Group	Test substance	Time-scale (Test type)	End point	Toxicity ¹ (mg/L)
Duckweed (<i>Lemna gibba</i>)	XDE-729 acid	7 d	E _y C ₅₀ E _r C ₅₀	15 (mm) >50 (mm)
Eurasian watermilfoil (<i>Myriophyllum spicatum</i>)	XDE-729 acid	14 d	E _y C ₅₀ E _r C ₅₀	0.0008 (nom) 0.00158 (nom)
Duckweed (<i>Lemna gibba</i>)	X11449757	7 d	E _y C ₅₀ E _r C ₅₀	>92.9 (mm) >92.9 (mm)
Eurasian watermilfoil (<i>Myriophyllum spicatum</i>)	X11449757	14 d	E _y C ₅₀ E _r C ₅₀	>0.1 (nom) >0.1 (nom)
Duckweed (<i>Lemna gibba</i>)	X11406790	7 d	E _y C ₅₀ E _r C ₅₀	>12 (mm) >12 (mm)
Eurasian watermilfoil (<i>Myriophyllum spicatum</i>)	X11406790	14 d	E _y C ₅₀ E _r C ₅₀	>0.1 (nom) >0.1 (nom)
Microcosm or mesocosm tests- NA				

It is indicated whether endpoints are based on nominal (nom), initial measured (im) or mean measured concentrations (mm).

¹ Endpoints for active stated in mg a.s./L. Endpoints for the representative formulation (GF-2573) stated in terms of mg formulation/L. All metabolite endpoints stated in terms of mg metabolite/L.

*blank formulation refers to the representative formulation without the active substance. XDE-729 acid is also known as the metabolite X11393729.

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

FOCUS Step1

Autumn application to winter cereals at 7.82 g a.s./ha

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC _{SW} (µg/L)	TER	Annex VI Trigger
a.s.	Fish	>1.33	Acute	1.197	>1111	100
a.s.	Fish	0.0115	Chronic	1.197	9.6	10
a.s.	Aquatic invertebrates	2.12	Acute	1.197	1771	100
a.s.	Aquatic invertebrates	0.144	Chronic	1.197	120	10

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC _{SW} (µg/L)	TER	Annex VI Trigger
a.s.	Marine crustacean	>1.3	Acute	1.197	>1086	100
a.s.	Marine crustacean	0.152	Chronic	1.197	127	10
a.s.	Gastropod mollusc	>1.21	Acute	1.197	>1011	100
a.s.	Algae	>0.245	Chronic	1.197	>205	10
a.s.	Higher plants - <i>Lemna</i>	2.13	Chronic	1.197	1779	10
a.s.	Higher plants - <i>Myriophyllum</i>	0.000149	Chronic	1.197	0.12	10
a.s.	Sediment-dwelling organisms	1.26	Chronic	1.197	1053	10
a.s.	Sediment-dwelling organisms	89.3 (mg/kg)	Chronic	11.1 (µg/kg)	8038	10
XDE-729 acid	Fish	>107	Acute	0.983	>108850	100
XDE-729 acid	Fish	11.8	Chronic	0.983	12004	10
XDE-729 acid	Aquatic invertebrates	>106	Acute	0.983	>107833	100
XDE-729 acid	Aquatic invertebrates	100	Chronic	0.983	101729	10
XDE-729 acid	Algae	23.0	Chronic	0.983	23398	10
XDE-729 acid	Higher plants- <i>Lemna</i>	15.0	Chronic	0.983	15259	10
XDE-729 acid	Higher plants- <i>Myriophyllum</i>	0.0008	Chronic	0.983	0.81	10
X11449757	Fish	>120	Acute	0.748	>160428	100
X11449757	Fish	8.9	Chronic	0.748	11898	10
X11449757	Aquatic invertebrates	>120	Acute	0.748	>160428	100
X11449757	Algae	4.13	Chronic	0.748	5521	10
X11449757	Higher plants- <i>Lemna</i>	>92.9	Chronic	0.748	>124198	10
X11449757	Higher plants- <i>Myriophyllum</i>	>0.1	Chronic	0.748	>134	10

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC _{SW} (µg/L)	TER	Annex VI Trigger
X11406790	Fish	>30	Acute	0.051	>588235	100
X11406790	Aquatic invertebrates	>30	Acute	0.051	>588235	100
X11406790	Algae	1.8	Chronic	0.051	35294	10
X11406790	Higher plants- <i>Lemna</i>	>12.0	Chronic	0.051	>235294	10
X11406790	Higher plants- <i>Myriophyllum</i>	>0.1	Chronic	0.051	>1961	10
GF-2573	Fish	78.7	Acute	5.814	13536	100
GF-2573	Aquatic invertebrates	14.0	Acute	5.814	2408	100
GF-2573	Algae	0.29	Chronic	5.814	50	10
GF-2573	Higher plants- <i>Lemna</i>	80	Chronic	5.814	>13760	10
GF-2573	Higher plants- <i>Myriophyllum</i>	0.0402	Chronic	5.814	6.9	10
GF-2573	Higher plants- <i>Myriophyllum</i>	0.0402	Chronic	1.576 (5m buffer)	26	10

FOCUS Step 2

Autumn application to winter cereals at 7.82 g a.s./ha, **Northern Europe** (worse-case than Southern)

Test substance	MS	Organism	Toxicity end point (mg/L)	Time scale	PEC _{SW} Max (µg/L)	TER	Annex VI Trigger
a.s.	N	Fish	0.0115	Chronic	0.412	28	10
a.s.	N	Higher plants ⁵ - <i>Myriophyllum</i>	0.000149	Chronic	0.412	0.36	10
XDE-729 acid	N	Higher plants ⁵ - <i>Myriophyllum</i>	0.0008	Chronic	0.536	1.5	10

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 3

Autumn application to winter cereals at 7.82 g a.s./ha

Test substance	Scenario and water body	Test organism	Time scale	Toxicity end point (mg/L)	PEC _{sw} Max (µg/L)	TER	Annex VI trigger
a.s.	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	0.050	3.0	10
	D1 stream				0.044	3.4	
	D2 ditch				0.050	3.0	
	D2 stream				0.043	3.5	
	D3 ditch				0.049	3.0	
	D4 pond				0.002	74.5	
	D4 stream				0.043	3.5	
	D5 pond				0.002	74.5	
	D5 stream				0.046	3.2	
	D6 ditch				0.050	3.0	
	R1 pond				0.003	49.7	
	R1 stream				0.035	4.3	
	R3 stream				0.046	3.2	
	R4 stream				0.041	3.6	
XDE-729 acid	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.0008	0.217	3.7	10
	D1 stream				0.136	5.9	
	D2 ditch				0.293	2.7	
	D2 stream				0.184	4.3	
	D3 ditch				0.0001	8000.0	
	D4 pond				0.024	33.3	
	D4 stream				0.043	18.6	
	D5 pond				0.028	28.6	
	D5 stream				0.045	17.8	
	D6 ditch				0.112	7.1	
	R1 pond				0.001	800.0	
	R1 stream				0.059	13.6	
	R3 stream				0.061	13.1	
	R4 stream				0.032	25.0	

Spring application to winter cereals at 6.25 g a.s./ha

Test substance	Scenario and water body	Test organism ³	Time scale	Toxicity end point (mg/L)	PEC _{sw} Max (µg/L)	TER	Annex VI trigger
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‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Test substance	Scenario and water body	Test organism ³	Time scale	Toxicity end point (mg/L)	PEC _{SW} Max (µg/L)	TER	Annex VI trigger
a.s.	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	0.040	3.7	10
	D1 stream				0.035	4.3	
	D2 ditch				0.039	3.8	
	D2 stream				0.030	5.0	
	D3 ditch				0.039	3.8	
	D4 pond				0.001	149.0	
	D4 stream				0.031	4.8	
	D5 pond				0.001	149.0	
	D5 stream				0.029	5.1	
	D6 ditch				0.040	3.7	
	R1 pond				0.001	149.0	
	R1 stream				0.026	5.7	
	R3 stream				0.037	4.0	
	R4 stream				0.026	5.7	
XDE-729 acid	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.0008	0.109	7.3	10
	D1 stream				0.068	11.8	
	D2 ditch				0.212	3.8	
	D2 stream				0.132	6.1	
	D3 ditch				0.0001	8000.0	
	D4 pond				0.001	800.0	
	D4 stream				0.002	400.0	
	D5 pond				0.024	33.3	
	D5 stream				0.055	14.5	
	D6 ditch				0.097	8.2	
	R1 pond				0.001	800.0	
	R1 stream				0.018	44.4	
	R3 stream				0.019	42.1	
	R4 stream				0.006	133.3	

Spring application to spring cereals at 6.25 g a.s./ha

Test substance	Scenario and water body	Test organism ³	Time scale	Toxicity end point (mg/L)	PEC _{SW} Max (µg/L)	TER	Annex VI trigger
a.s.	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	0.039	3.8	10
	D1 stream				0.031	4.8	
	D3 ditch				0.039	3.8	
	D4 pond				0.001	149.0	
	D4 stream				0.033	4.5	
	D5 pond				0.001	149.0	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Test substance	Scenario and water body	Test organism ³	Time scale	Toxicity end point (mg/L)	PEC _{SW} Max (µg/L)	TER	Annex VI trigger
	D5 stream				0.031	4.8	
	R4 stream				0.026	5.7	
XDE-729 acid	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.0008	0.015	53.3	10
	D1 stream				0.017	47.1	
	D3 ditch				0.0001	8000.0	
	D4 pond				0.001	800.0	
	D4 stream				0.001	800.0	
	D5 pond				0.0001	8000.0	
	D5 stream				0.0001	8000.0	
	R4 stream				0.027	29.6	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

FOCUS Step 4

Autumn application to winter cereals at 7.82 g a.s./ha

Test substance	Scenario and water body	Test organism	Time scale	Toxicity end point (mg/L)	Buffer zone distance	PEC _{SW} Max (µg/L)	TER	Annex VI trigger
a.s.	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	5m (drift reduction only)	0.014	10.6	10
	D1 stream					0.016	9.3	
	D2 ditch					0.014	10.6	
	D2 stream					0.016	9.3	
	D3 ditch					0.013	11.5	
	D4 pond					0.001	149.0	
	D4 stream					0.016	9.3	
	D5 pond					0.001	149.0	
	D5 stream					0.017	8.8	
	D6 ditch					0.014	10.6	
	R1 pond					0.003	49.7	
	R1 stream					0.035	4.3	
	R3 stream					0.041	3.6	
	R4 stream					0.041	3.6	
a.s.	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	10m (drift and runoff reduction)	0.007	21.3	10
	D1 stream					0.008	18.6	
	D2 ditch					0.007	21.3	
	D2 stream					0.008	18.6	
	D3 ditch					0.007	21.3	
	D4 pond					0.001	149.0	
	D4 stream					0.008	18.6	
	D5 pond					0.001	149.0	
	D5 stream					0.009	16.6	
	D6 ditch					0.009	16.6	
	R1 pond					0.001	149.0	
	R1 stream					0.016	9.3	
	R3 stream					0.019	7.8	
	R4 stream					0.018	8.3	
a.s.	R1 pond	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	20m (drift and runoff reduction)	0.001	149.0	10
	R1 stream					0.008	18.6	
	R3 stream					0.010	14.9	
	R4 stream					0.010	14.9	

Mitigation not possible to reduce exposure via drainage to XDE-729 acid metabolite.

Spring application to winter cereals at 6.25 g a.s./ha

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Test substance	Scenario and water body	Test organism	Time scale	Toxicity end point (mg/L)	Buffer zone distance	PEC _{SW} Max (µg/L)	TER	Annex VI trigger
a.s.	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	5m (drift reduction only)	0.011	13.5	10
	D1 stream					0.013	11.5	
	D2 ditch					0.011	13.5	
	D2 stream					0.011	13.5	
	D3 ditch					0.010	14.9	
	D4 pond					0.001	149.0	
	D4 stream					0.011	13.5	
	D5 pond					0.001	149.0	
	D5 stream					0.010	14.9	
	D6 ditch					0.011	13.5	
	R1 pond					0.001	149.0	
	R1 stream					0.020	7.5	
	R3 stream					0.018	8.3	
	R4 stream					0.016	9.3	
a.s.	R1 pond	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	10m (drift and runoff reduction)	0.001	149.0	10
	R1 stream					0.009	16.6	
	R3 stream					0.008	18.6	
	R4 stream					0.007	21.3	

Mitigation not possible to reduce exposure via drainage to XDE-729 acid metabolite.

Spring application to spring cereals at 6.25 g a.s./ha

Test substance	Scenario and water body	Test organism	Time scale	Toxicity end point (mg/L)	Buffer zone distance	PEC _{SW} Max (µg/L)	TER	Annex VI trigger
a.s.	D1 ditch	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	5m (drift reduction only)	0.011	13.5	10
	D1 stream					0.011	13.5	
	D3 ditch					0.011	13.5	
	D4 pond					0.001	149.0	
	D4 stream					0.012	12.4	
	D5 pond					0.001	149.0	
	D5 stream					0.011	13.5	
	R4 stream					0.018	8.3	
a.s.	R4 stream	Higher plants- <i>Myriophyllum</i>	Chronic	0.000149	10m (drift and runoff reduction)	0.008	18.6	10

Mitigation not possible to reduce exposure via drainage to XDE-729 acid metabolite.

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Bioconcentration				
	a.s.	XDE-729 acid	X11449757	X11406790
logP _{O/W}	3.76	-0.83	<0.3	<0.3
Bioconcentration factor (BCF) ^{1 ‡}	217*	-	-	-
Annex VI Trigger for the bioconcentration factor	1000	-	-	-
Clearance time -days (CT ₉₅)	1.6	-	-	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	<MQR	-	-	-

¹ only required if log P_{O/W} >3.* based on total ¹⁴C or on specific compounds

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Test substance	Acute oral toxicity (LD ₅₀ µg/bee)	Acute contact toxicity (LD ₅₀ µg/bee)
a.s. ‡	>108	>98.1
Preparation ¹	>215.6	>200
Field or semi-field tests - NA		

¹ as preparation

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Cereals at 0.00782 kg a.s./ha

Test substance	Route	Hazard quotient	Annex VI Trigger
a.s.	Contact	0.08	50
a.s.	oral	0.07	50
Preparation	Contact	4.54	50
Preparation	oral	4.21	50

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Laboratory tests with standard sensitive species

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Species	Test Substance	End point	Effect (LR ₅₀ g/ha ¹)
<i>Typhlodromus pyri</i> ‡	GF-2573	Mortality	>1814
<i>Aphidius rhopalosiphi</i> ‡	GF-2573	Mortality	1462

¹ as preparation, assuming preparation density of 0.907 g/cm³

Cereals at 0.00782 g a.s./ha

Test substance	Species	Effect (LR ₅₀ g/ha)	HQ in-field	HQ off-field ¹	Trigger
GF-2573	<i>Typhlodromus pyri</i>	>1814	0.53	0.01	2
GF-2573	<i>Aphidius rhopalosiphi</i>	1462	0.62	0.02	2

¹ assuming 1m distance to field edge, 2.77% spray drift

Further laboratory and extended laboratory studies – NA
Field or semi-field tests - NA

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point
Earthworms			
<i>Eisenia fetida</i>	a.s. ‡	Acute 14 days	LC _{50 corr} = 500 mg a.s./kg d.w.soil
<i>Eisenia fetida</i>	a.s. ‡	Chronic 8 weeks	NOEC _{corr} = 5.0 mg a.s./kg d.w.soil
<i>Eisenia fetida</i>	GF-2573	Acute	LC _{50 corr} > 500 mg/kg d.w.soil ¹
<i>Eisenia fetida</i>	GF-2573	Chronic	NOEC _{corr} = 600 mg/kg d.w.soil ¹
<i>Eisenia fetida</i>	XDE-729 acid	Acute	LC ₅₀ > 1000 mg/kg d.w.soil
<i>Eisenia fetida</i>	XDE-729 acid	Chronic	NOEC = 10 mg/kg d.w.soil
<i>Eisenia fetida</i>	X11449757	Acute	LC ₅₀ > 1000 mg/kg d.w.soil
<i>Eisenia fetida</i>	X11449757	Chronic	NOEC = 10 mg/kg d.w.soil
<i>Eisenia fetida</i>	Non-extractable residues of a.s.	Chronic	NOEC = 7.10 mg non-extractable residues/kg d.w.soil
Other soil macro-organisms			
<i>Hypoaspis aculeifer</i>	a.s. ‡	Chronic	NOEC _{corr} = 12.5 mg a.s./kg d.w.soil
<i>Hypoaspis aculeifer</i>	XDE-729 acid	Chronic	NOEC = 12.5 mg /kg d.w.soil
<i>Hypoaspis aculeifer</i>	X11449757	Chronic	NOEC = 25 mg /kg d.w.soil
Collembola			
<i>Folsomia candida</i>	a.s. ‡	Chronic	NOEC _{corr} = 500 mg a.s./kg d.w.soil
<i>Folsomia candida</i>	XDE-729 acid	Chronic	NOEC = 25 mg /kg d.w.soil
<i>Folsomia candida</i>	X11449757	Chronic	NOEC = 10 mg /kg d.w.soil
Soil micro-organisms			
Nitrogen mineralisation	a.s. ‡	28 days	< 25% effect at day 28 at 0.0535 mg a.s./kg d.w.soil
Nitrogen mineralisation	GF-2573	28 days	< 25% effect at day 28 at 6.037 mg/kg d.w.soil ¹
Nitrogen mineralisation	XDE-729 acid	28 days	< 25% effect at day 28 at 0.05 mg/kg d.w.soil
Nitrogen mineralisation	X11449757	28 days	< 25% effect at day 28 at 0.052 mg/kg d.w.soil

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Test organism	Test substance	Time scale	End point
Carbon mineralisation	a.s. ‡	28 days	< 25% effect at day 28 at 0.0535 mg a.s./kg d.w.soil
Carbon mineralisation	GF-2573	28 days	< 25% effect at day 28 at 6.037 mg/kg d.w.soil ¹
Carbon mineralisation	XDE-729 acid	28 days	< 25% effect at day 28 at 0.05 mg/kg d.w.soil
Carbon mineralisation	X11449757	28 days	< 25% effect at day 28 at 0.052 mg/kg d.w.soil
Field studies ² - NA			

¹ endpoint in terms of preparation² litter bag, field arthropod studies not included at 8.3.2/10.5 above, and earthworm field studies

Toxicity/exposure ratios for soil organisms

Crop and application rate

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Earthworms					
<i>Eisenia fetida</i>	a.s. ‡	Acute	0.009 (maximum initial)	55556	10
<i>Eisenia fetida</i>	a.s. ‡	Chronic	0.009 (maximum initial)	556	5
<i>Eisenia fetida</i>	GF-2573	Acute	0.905(maximum initial)	552	10
<i>Eisenia fetida</i>	GF-2573	Chronic	0.905(maximum initial)	663	5
<i>Eisenia fetida</i>	XDE-729 acid	Acute	0.009 (peak accumulation)	111111	10
<i>Eisenia fetida</i>	XDE-729 acid	Chronic	0.009 (peak accumulation)	1111	5
<i>Eisenia fetida</i>	X11449757	Acute	0.0025 (peak accumulation)	400000	10
<i>Eisenia fetida</i>	X11449757	Chronic	0.0025 (peak accumulation)	4000	5
<i>Eisenia fetida</i>	NER*	Chronic	0.012 (mg parent.kg)	592	5

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Other soil macro-organisms					
Soil mite	a.s. ‡	Chronic	0.009 (maximum initial)	1389	5
	XDE-729 acid	Chronic	0.009 (peak accumulation)	1389	5
	X11449757	Chronic	0.0025 (peak accumulation)	10000	5
Collembola	a.s. ‡	Chronic	0.009 (maximum initial)	55556	5
	XDE-729 acid	Chronic	0.009 (peak accumulation)	2778	5
	X11449757	Chronic	0.0025 (peak accumulation)	4000	5

*NER-Non extractable residues

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Preliminary screening data

Not required for herbicides as ER₅₀ tests should be provided

Laboratory dose response tests

Most sensitive species	Test substance	ER ₅₀ (g/ha) vegetative vigour	ER ₅₀ (g/ha) emergence	Exposure ¹ (g/ha)	TER (veg vig)	TER (emergence)	Trigger
Soybean / carrot	GF-2573	0.4 ²	0.417 ²	0.217(1m) ²	1.92	2.00	5
				0.045 (5m) ²	9.36	9.75	
Carrot	XDE-729 acid	-	0.3835 ²	0.210 (1m) ²	-	1.85	5
				0.043 (5m) ²		8.97	
NA ³	X11449757	-	>15.0	0.207 (1m)	-	>72.2	5

¹ Assuming spray drift of 2.77% (1m from field edge) or 0.57% (5m from field edge) – Rautmann et al. 2001

² g a.e./ha (grams as acid equivalent/ha)

³ All 11 species tested < 50% effects at maximum tested rate.

Additional studies (e.g. semi-field or field studies)

NA

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	end point
Activated sludge (<i>Pseudomonas</i> sp)	EC ₅₀ > 981 mg a.s./L

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

Compartment	
soil	XDE-729 methyl (a.s.), XDE-729 acid, X11449757
water	XDE-729 methyl (a.s.), XDE-729 acid, X11449757, X11406790, photolysis metabolites 'deg 10' 'deg 11' and 'deg 14'
sediment	XDE-729 methyl (a.s.), XDE-729 acid, X11449757, X11406790
groundwater	-

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

List of end points (based on EPCO Manual E4 - rev. 4 (September 2005))

Rapporteur Member State	Month and year	Active Substance (Name)
United Kingdom	December 2013	XDE-729 Methyl (Halauxifen-methyl)

Ecotoxicology

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

Active substance (XDE-729 methyl)

RMS/peer review proposal

R50/53

H400/H410

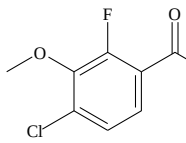
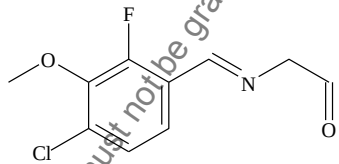
Preparation (GF-2573)

RMS/peer review proposal

R50/53

H410

Code/Trivial name	Chemical name	Structural formula
XDE-729 methyl X11393728 XDE-729 ME XDE-729 ME PAI XDE-729 Methyl Ester XDE-728 XR-729	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate (former IUPAC name for XDE-729 methyl) 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-pyridine-2-carboxylic acid methyl ester	
XDE-729 acid X11393729 XDE-729 TGAI XDE-729 XR-729	4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (former IUPAC name for XDE-729 acid) 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-pyridine-2-carboxylic acid	
X11406790	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)pyridine-2-carboxylate	
X11449757	4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-pyridine-2-carboxylic acid	
Deg 10	methyl 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-3-hydroxypyridine-2-carboxylate	 or isomer

Code/Trivial name	Chemical name	Structural formula
Deg 11	methyl (2E)-3-aza-4-(4-chloro-2-fluoro-3-methoxyphenyl)-4-oxobut-2-enoate	 or isomer
Deg 14	(3E)-3-aza-4-(4-chloro-2-fluoro-3-methoxyphenyl)but-3-enal	 or isomer