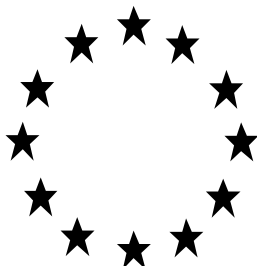


Draft Renewal Assessment Report
under Regulation (EC) 1107/2009



FORAMSULFURON
Volume 3 – B.5 (PPP) –
foramsulfuron+isoxadifen-ethyl OD 45
(22.5+22.5 g/L)

Rapporteur Member State: Finland
Co-Rapporteur Member State: Slovakia

March 2015

Volume 1

Level 1: Statement of subject matter and purpose for which this report has been prepared and background information on the application

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Level 3: Proposed decision with respect to the application

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Annex C: Confidential information and, where relevant, details of any task force formed for the purpose of generating tests and studies submitted

List of Endpoints

Version History

When	What
2015/March	First Draft RAR

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B.5. METHODS OF ANALYSIS

This dossier contains study reports already submitted by Bayer CropScience for the Annex I inclusion of foramsulfuron, as well as new data, not yet evaluated at EU level and that was considered by the applicant to be necessary for the renewal of approval of foramsulfuron. In order to distinguish these, reference to studies in the original dossier are depicted in grey.

For summaries of studies submitted during the frame of the first Annex I inclusion please refer to the corresponding section in the Monograph. Copies of the study reports are provided in the baseline dossier provided by Bayer CropScience. Additional studies which were not submitted during the Annex I inclusion process are provided in the dossier and summarized in this document.

B.5.1. METHODS USED FOR THE GENERATION OF PRE-AUTHORISATION DATA

Samples (preparation, analytical standards, active substances as manufactured, analytical standards for metabolites, reference substances for relevant impurities) will be provided upon request.

B.5.1.1. Analysis of the plant protection product

B.5.1.1.1 Methods for the determination of the active substance and/or variant in the plant protection product

Method

The two reports (KCP 5.1.1/01 and 5.1.1/02) below were present in the original dossier submitted for the approval of foramsulfuron at European level. The method was developed to analyse several active substances in the formulation. Since the European approval in 2002, a new method has been developed that is specific for foramsulfuron and the safener, isoxadifen-ethyl, in the formulation and is state of the art.

Report:	KCP 5.1.1/01; Müller, Th.; 1999; M-187770-01; CHE-2000-997
Title:	Determination of AE F130360, AE F115008 and AE F122006 in combination formulated products by liquid chromatography (HPLC); AE F130360; Code: AE F130360 02 WG62 A1
Report No:	C007136; AL054/99-0
Document No:	M-187770-01-2
Guidelines:	US EPA OPPTS 830.1700; EU 91/414/EEC Annex III 5.1; Deviation not specified
GLP/GEP:	No

Validation

Report:	KCP 5.1.1/02; Müller, Th.; 1999; M-188910-01; CHE-2000-998
Title:	Validation of the analytical method AL054/99-0 for the determination of AE F115008 (Iodosulfuron-methyl-sodium), AE F130360 and AE F122006 in AE F130360 02 WG62 A1 and AE F130360 02 WG61 A1 and of AE F122006 and AE F130360 in AE F130360 01 WG70 A1 and AE F130360 01 1K05 A3
Report No:	C004973; PA99/016
Document No:	M-188910-01-1
Guidelines:	EU 91/414/EEC Annex III 5.1; US EPA OPPTS 830.1700; Deviation not specified
GLP/GEP:	Yes

An analytical method (AM021113MF1) has been developed for the determination of the active substance foramsulfuron and the safener isoxadifen-ethyl in formulations.

Report:	KCP 5.1.1 /03;Michel, A.;2013;M-467137-01
Title:	Determination of foramsulfuron and isoxadifen-ethyl in formulations ; Assay - HPLC, external standard
Report No:	AM021113MF1
Document No:	M-467137-01-1
Guidelines:	REGULATION (EC) No 1107/2009 , Comission Regulation 545/2011, 5.1 US EPA OCSPP 830.1800;Deviation not specified
GLP/GEP:	no

Material and Methods:

A sample of formulated product (containing the active substances at the concentration used for the calibration: approx. 20 mg foramsulfuron and 20 mg isoxadifen-ethyl) is extracted in a 100 mL volumetric flask with 40 mL of a triethylamine solution (0.01 mol/L adjusted to pH 7 with phosphoric acid) plus 40 mL of acetonitrile, in an ultrasonic bath, then completed to volume with acetonitrile. 5 µL of this solution is injected onto the HPLC column.

The active substances are separated by HPLC chromatography using a C18 stationary phase (Symmetry C18, particle size 5 µm, stainless steel column 100*4.6 mm) at 35 °C. Active substances are detected by UV absorption at 275 nm (foramsulfuron) then 250 nm (isoxadifen-ethyl) after gradient elution with a mixture acetonitrile/phosphoric acid 0.01 mol/L at a flow-rate of 2.0 mL/min.

Quantification is carried out by comparison of the peak area of the sample with that of the corresponding reference substances (external standard quantification).

Validation

Report:	KCP 5.1.1 /04;Kienow, A. ; Michel, A.;2013;M-468476-01
Title:	Validation of HPLC-method AM021113MF1 - Determination of foramsulfuron and isoxadifen-ethyl in formulations - foramsulfuron + isoxadifen-ethyl OD 45 (22.5+22.5 g/L)
Report No:	VB1-AM021113MF1
Document No:	M-468476-01-1
Guidelines:	REGULATION (EC) No 1107/2009 , Comission Regulation 545/2011, 5.1, SANCO/3030/99 rev. 4, US EPA OCSPP 830.1800;Deviation not specified
GLP/GEP:	no

Specificity	Comparison of UV spectra and retention times from items and sample. Reference substances of the active substances, solutions of the blank formulation were run to the method conditions to determine any co-elutions and to demonstrate the specificity of the method.	
Interference	No interferences with the analytical method were observed.	
Linearity	For determination of the linear working range for the active substances, 6 solutions of the reference substances were prepared so that the working range for the active substances was included.	
	Compound	Linearity
	foramsulfuron (6 solutions)	range : 106.2 - 302.4 mg/L; 50-150% of expected conc. y = 0.2134 x + 0.0195 multip. correlation coefficient: $r_k = 0.99994$
	isoxadifen-ethyl (6 solutions)	range : 102.3 - 306.5 mg/L; 50-150% of expected conc. y = 0.5224 x - 0.0032 multip. correlation coefficient: $r_k = 0.99999$

Accuracy/Recovery	Accuracy was determined by analysis of 6 independent solutions in which known amounts of the reference substances were added to a blank formulation. The accuracy result is expressed as the recovery rate as well as the relative standard deviation for the active substances.	
	Compound	Accuracy
	foramsulfuron	mean recovery: 100.9 %; RSD: 0.3 % (6 solutions, no outlier)
	isoxadifen-ethyl	mean recovery: 98.4 %; RSD: 0.6 % (6 solutions, no outlier)
Precision/Repeatability	Repeatability was evaluated by analysing the active substances in 6 independent preparations in the formulated product.	
	Compound	Repeatability
	foramsulfuron	RSD: 0.21 % at mean: 2.31 % (6 solutions, no outlier)
	isoxadifen-ethyl	RSD: 0.36 % at mean: 2.28 % (6 solutions, no outlier)

Conclusion: The method for the determination of foramsulfuron and isoxadifen-ethyl in the formulation coded specification 102000011304-06 was found to be valid.

B.5.1.1.2 Method for the degradation products in the formulation:

During the accelerated storage study, a decrease of the content in Foramsulfuron has been noted. Therefore, degradation products were determined before and after storage.

Report:	KCP 5.1.1 /05;Michel, A.;2013;M-460493-01
Title:	Determination of foramsulfuron byproduct AE F092944, AE F153745 and AE F130619 in formulations ; Assay HPLC, external standard
Report No:	AM020213MF1
Document No:	M-460493-01-1
Guidelines:	REGULATION (EC) No 1107/2009 , Comission Regulation 545/2011, 5.1 US EPA OCSP 830.1800;Deviation not specified
GLP/GEP:	no

The analytical method for the analysis of 3 degradation products in the formulation has been validated.

Description

A sample of formulation, estimated to contain the same concentrations in degradation products as in the reference solution (for example 0.3 mg of AE F092944, 0.7 mg of AE F153745 and 0.4 mg of AE F130619), is weighed into a volumetric flask (100 mL) and dissolved with a mixture acetonitrile / triethylamine (0.02 mol/L solution adjusted with phosphoric acid to pH 7), 30/70. Adjustment to 100 mL is made with the same mixture after sonication. 5 µL of this solution is injected into the chromatograph.

The separation between the active substances and the impurities is achieved by high performance liquid chromatography using a reversed phase column (Symmetry C18, 3.5 µm, 100 x 4.6 mm ID) eluted with a mixture of acetonitrile/water + phosphoric acid 0.01 mol/L (gradient elution) at a flow-rate of 2 mL/min and a temperature of 30 °C. Compounds are detected in the eluate by UV absorption at 235 nm.

Validation

The HPLC method AM020213MF1 was validated for the formulation by checking the parameters specificity and interference from excipients, linearity, accuracy/recovery, precision/repeatability.

Report:	KCP 5.1.1 /06;Kienow, A. ; Michel, A.;2013;M-471234-01
Title:	Validation of HPLC-method AM020213MF1 - Determination of foramsulfuron byproducts AE F092944, AE F153745 and AE F130619 in formulations - foramsulfuron + isoxadifen-ethyl OD 45 (22.5+22.5 g/L)
Report No:	VB2-AM020213MF1
Document No:	M-471234-01-1
Guidelines:	REGULATION (EC) No 1107/2009 , Comission Regulation 545/2011, 5.1, SANCO/3030/99 rev. 4;Deviation not specified
GLP/GEP:	no

Specificity	Reference substances, solutions of the blank formulation were run to the method conditions to determine any co-elutions and to demonstrate the specificity of the method. The UV spectra show no spectral difference. Retention times are identical.	
Interference	No interferences for the determination of AE F092944, AE F153745 and AE F130619 with the analytical method were observed.	
Linearity	For determination of the linear working range for the substances, solutions of the reference substances were prepared so that the working range was included.	
	Compound	Linearity
	AE F092944 (8 concentrations)	range: 4.1 - 12.2 mg/L; 50-150% of expected conc. $y = 0.3459x + 0.0013$ multip. correlation coefficient: $r_k = 0.99931$
	AE F153745 (8 concentrations)	range: 4.6 - 13.7 mg/L; 50-150% of expected conc. $y = 0.841x + 0.0204$ multip. correlation coefficient: $r_k = 0.99980$
	AE F130619 (8 concentrations)	range: 2.5 - 7.45 mg/L; 50-150% of expected conc. $y = 1.2159x + 0.0181$ multip. correlation coefficient: $r_k = 0.99988$
Accuracy/Recovery	Accuracy was determined by analysis of 6 independent solutions in which known amounts of the reference substances were added to a laboratory prepared synthetic formulation. The accuracy result is expressed as the recovery rate as well as the relative standard deviation for the active substances.	
	Compound	Accuracy (recovery / RSD)
	AE F092944	mean recovery: 99.2 %; RSD: 0.69 % (6 solutions, no outlier)
	AE F153745	mean recovery: 100.7 %; RSD: 0.70 % (6 solutions, no outlier)
	AE F130619	mean recovery: 100.5 %; RSD: 0.90 % (6 solutions, no outlier)
Precision/Repeatability	Repeatability was evaluated by analysing 5 independent preparations of the formulated product. All results acceptable with regards to the Horwitz equation.	
	Compound	Repeatability (RSD)
	AE F092944	RSD: 2.62 % at mean: 0.012% (5 solutions, no outlier)
	AE F153745	RSD: 3.41 % at mean: 0.016 % (5 solutions, no outlier)
	AE F130619	RSD: 0.66 % at mean: 0.007 % (5 solutions, no outlier)

Conclusion: The method AM020213MF1 for the determination of degradation products AE F092944, AE F153745 and AE F130619 in the formulation coded specification 102000011304 was found to be valid. The test has been performed in a GLP test facility but the test itself has not been performed according to GLP. However, as the validation is done in compliance with SANCO/3030/99 rev. 4, the missing GLP is considered as a minor data gap.

B.5.1.1.3 Applicability of existing CIPAC methods

There is no CIPAC method available for the determination of foramsulfuron or for isoxadifen-ethyl (safener).

B.5.1.1.4 Methods for determination of relevant impurities identified in the technical material or which may be formed during manufacture of the plant protection product or from degradation of the plant protection product during storage

No analytical methods for determination of the organic impurities were developed for the formulated product since no toxicologically or eco-toxicologically relevant impurities are expected to be formed during the formulation process.

B.5.1.1.5 Methods for the determination of relevant co-formulants or components of co-formulants, where required by the national competent authorities

With respect to toxicological, eco-toxicological or environmental aspects the product does not contain any relevant formulants. Therefore, a special analytical method and validation is not needed.

B.5.1.2. Methods for the determination of residues

There are no additional methods for the determination of residues in any matrix. All methods have been included in the active substance dossier.

B.5.2. METHODS FOR POST-APPROVAL CONTROL AND MONITORING PURPOSES

There are no additional methods for the determination of residues in any matrix. All methods have been included in the active substance dossier.

B.5.3. REFERENCES RELIED ON

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company name, Report No., Date, GLP status (where relevant), published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
B.1.1.1. KCP 5.1.1 /01	Mueller, T.	1999	Determination of AE F130360, AE F115008 and AE F122006 in combination in formulated products by liquid chromatography (HPLC) (analytical method) AE F130360 Code: AE F130360 02 WG62 A1 Hoechst Schering AgrEvo GmbH, Frankfurt am Main, Germany Bayer CropScience, Report No.: C007136, Edition Number: M-187770-01-2 EPA MRID No.: 45417202 Date: 1999-06-17 GLP/GEP: no, unpublished	N	N	Not relevant	Bayer CropScience	In DAR 2001
B.5.1.1.1 KCP 5.1.1 /02	Mueller, T.	1999	Validation of the analytical method AL054/99-0 for the determination of AE F115008 (iodosulfuron-methyl-sodium), AE F130360 and AE F122006 in AE F130360 02 WG62 A1 and AE F130360 02 WG61 A1 and of AE F122006 and AE F130360 in AE F130360 01 Hoechst Schering AgrEvo GmbH, Frankfurt am Main, Germany Bayer CropScience, Report No.: C004973, Edition Number: M-188910-01-1 Date: 1999-08-10 GLP/GEP: yes, unpublished	N	N	Not relevant	Bayer CropScience	In DAR 2001
B.5.1.1.1 KCP 5.1.1 /03	Michel, A.	2013	Determination of foramsulfuron and isoxadifen-ethyl in formulations ; Assay - HPLC, external standard Bayer CropScience, Report No.: AM021113MF1, Edition Number: M-467137-01-1 Date: 2013-10-08 GLP/GEP: no, unpublished	N	N	Not relevant	Bayer CropScience	Submitted for the purpose of renewal

B.5.1.1.1. KCP 5.1.1 /04	Kienow, A. ; Michel, A.	2013	Validation of HPLC-method AM021113MF1 – Determination of foramsulfuron and isoxadifen-ethyl in formulations- foramsulfuron + isoxadifen-ethyl OD 45 (22.5+22.5 g/L) Bayer CropScience, Bayer CropScience, Report No.: VB1-AM021113MF1, Edition Number: M-468476-01-1 Date: 2013-10-30 GLP/GEP: no, unpublished	N	N	Not relevant	Bayer CropScience	Submitted for the purpose of renewal
B.5.1.1.2. KCP 5.1.1 /05	Michel, A.	2013	Determination of foramsulfuron byproduct AE F092944, AE F153745 and AE F130619 in formulations ; Assay HPLC, external standard Bayer CropScience, Report No.: AM020213MF1, Edition Number: M-460493-01-1 Date: 2013-07-17 GLP/GEP: no, unpublished	N	N	Not relevant	Bayer CropScience	Submitted for the purpose of renewal
B.5.1.1.2. KCP 5.1.1 /06	Kienow, A. ; Michel, A	2013	Validation of HPLC-method AM020213MF1 - Determination of foramsulfuron byproducts AE F092944, AE F153745 and AE F130619 in formulations - foramsulfuron + isoxadifen-ethyl OD 45 (22.5+22.5 g/L) Bayer CropScience, Report No.: VB2-AM020213MF1, Edition Number: M-471234-01-1 Date: 2013-12-02 GLP/GEP: no, unpublished	N	N	Not relevant	Bayer CropScience	Submitted for the purpose of renewal