

European Commission



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

ETHOFUMESATE

Volume 1

Rapporteur Member State: Austria
Co-Rapporteur Member State: Denmark

Version History

When	What
1998	Initial DAR (no addenda to Volume 1 could be identified)
2015/01	DRAR

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Level 1

ETHOFUMESATE

1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1. CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1. Purpose for which the draft assessment report was prepared

Ethofumesate was originally included in Annex I of the EU Council Directive 91/414/EEC with Commission Directive 2002/37/EC (entry into force on 1 March 2003). The active substance was subsequently approved under Regulation (EC) 1107/2009 via Implementing Regulation (EU) 540/2011. In accordance with Commission Regulation (EU) 844/2012 of 18 September 2012, United Phosphorus Limited (UPL) and the Task Force Ethofumesate (representing Bayer CropScience and Adama Deutschland GmbH (former Feinchemie Schwebda GmbH)) submitted separate dossiers to support the renewal of the approval of Ethofumesate. Austria acting as the Rapporteur Member State (RMS) evaluated all aspects of the renewal dossiers via a Draft Renewal Assessment Report (DRAR). The DRAR was the subject of a peer review by the Co-RMS Denmark. This DRAR provides a discussion of relevant new studies and information submitted and evaluated since the first approval of Ethofumesate in 2003. Regarding studies submitted for the original approval mostly re-wording was conducted and additional information was included in DRAR where considered necessary for better overview. Finally, the validity of studies in view of updated OECD guidelines was proven.

No proposal for MRL setting is included in the DRAR.

The RMS also paid attention to new criteria for classification and labelling according to Regulation (EC) 1272/2008. The outcome of the Meeting of the Commission Working Group on the Classification and Labelling of Dangerous Substances Pesticides, ECB Ispra, 19-21 May 1999 (ECBI/43/99 Rev. 2), that no classification and labelling for ethofumesate is necessary for human health, could be further supported. Regarding ecotoxicity, new proposal for classification and labelling has been established (H400 and H410 instead of current H411), based on the new studies with adverse endpoints included in the supplementary dossier for the renewal.

1.1.2. Arrangements between rapporteur Member State and co-rapporteur Member State

According to an agreement reached by the respective designated authorities, the RMS Austria conducted the full evaluation and prepared the DRAR. The Co-RMS Denmark reviewed the DRAR for commenting. After further evaluation taking into account the received comments from Denmark and the notifiers the first official version of the DRAR was submitted to the Commission and EFSA by end of January 2015.

1.1.3. EU Regulatory history for use in Plant Protection Products

Ethofumesate was one of the 90 substances covered by the Commission Regulation (EEC) No 3600/92 from 11 December 2002 laying down the detailed rules for the implementation of the first stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC.

In accordance with the provisions of Article 5 of Regulation (EEC) No 3600/92, the Commission designated Sweden as rapporteur Member State to carry out the assessment of Ethofumesate on the basis of the dossiers submitted by the notifiers.

Hoechst Schering AgrEvo GmbH, Feinchemie Schwebda GmbH, Barclay Chemicals Manufacturing Exports Ltd and Phytorus SA submitted a dossier to the rapporteur Member State. Hoechst Schering AgrEvo GmbH and Feinchemie Schwebda GmbH were the main data submitters, with a joint dossier which did not contain substantial data gaps, taking into account the supported uses. Barclay Chemicals Manufacturing Exports Ltd and Phytorus SA did not submit complete dossiers. Information has not been submitted by third parties.

In accordance with the provisions of Article 7(1) of Regulation (EEC) No 3600/92, Sweden submitted on 2 October 1998 to the Commission the report of its examination, including, as required, a recommendation concerning the possible inclusion of ethofumesate in Annex I to the Directive. Moreover, in accordance with the same provisions, the Commission and the Member States received also the summary dossier on ethofumesate from Hoechst Schering AgrEvo GmbH and Feinchemie Schwebda GmbH, on 10 March 1999.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the Commission forwarded for consultation the draft assessment report to all the Member States on 14 December 1998 as well as to Hoechst Schering AgrEvo GmbH and Feinchemie Schwebda GmbH being the main data submitters, on 15 December 1998.

The meetings for the consultations were organised on behalf of the Commission by the Biologische Bundesanstalt für Land und Forstwirtschaft (BBA) in Braunschweig, Germany, from March to October 1999.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the dossier, the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications on the remaining issues, received after the peer review were referred to the Standing Committee on the Food Chain and Animal Health, and specialised working groups of this Committee, for final examination, with participation of experts.

The overall conclusions of the evaluation of ethofumesate, as finalised by the Standing Committee on Plant Health on 15 May 2002, were provided in the Review Report (Ethofumesate, SANCO/6503/VI/99-final).

In agreement with Article 3 of Regulation (EC) No 844/2012 Task Force Ethofumesate (representing Bayer CropScience and Adama Deutschland GmbH (former Feinchemie Schwebda GmbH)), United Phosphorus Limited and Hermoo Belgium NV submitted applications for renewal to Austria as RMS and Denmark as Co-RMS by the deadline of 31 July 2013. All three applications were considered complete.

Task Force Ethofumesate and United Phosphorus Limited submitted their supplementary dossiers by the deadline for submission (31 January 2014). As required by Article 8 of Regulation (EC) No 844/2012 RMS checked the supplementary dossiers for their completeness. It was concluded that both supplementary dossiers completely fulfil the requirements set out in Article 7 of the Regulation (EC) No 844/2012. No dossier has been submitted by Hermoo Belgium NV.

From the first approval of Ethofumesate (2003) no EFSA conclusion exists.

Reasoned opinion on the review of the existing maximum residue levels (MRLs) for ethofumesate according to Article 12 of Regulation (EC) No 396/2005 from 2012 is available (<http://www.efsa.europa.eu/en/efsajournal/doc/2959.pdf>).

1.1.4. Evaluations carried out under other regulatory contexts

Ethofumesate is used only as herbicide and not regulated by other EU legislations ((e.g. biocides, flavourings, food additives, cosmetics).

The evaluation of the US EPA can be found under <http://www.epa.gov/oppsrrd1/reregistration/ethofumesate/>.

The evaluation of the PMRA (mainly based on the evaluation of the US EPA) can be found under http://publications.gc.ca/collections/collection_2007/pmra-arla/H113-27-2007-12E.pdf

Ethofumesate has not been considered by the JMPR.

FAO specification is available under:

http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Ethofumesate07.pdf

Ethofumesate is currently included in Annex VI of Regulation (EC) No 1272/2008 with Index No 607-314-00-2 (CAS No: 26225-79-6) as Aquatic Chronic 2, H411.

1.2. APPLICANT INFORMATION

1.2.1. Name and address of applicant(s) for approval of the active substance

Task Force Ethofumesate:

Address: Bayer S.A.S
Bayer CropScience
16 rue Jean-Marie Leclair
CS 90106
69266 Lyon Cedex 09
France

Task Force Members: Bayer CropScience AG
Alfred-Nobel-Strasse 50
40789 Monheim
Germany

Adama Deutschland GmbH (former Feinchemie Schwebda GmbH)
Edmund Rumpler Strasse 6
51149 Cologne
Germany

United Phosphorus Limited (UPL) Europe Ltd:

Address: UPL Europe Ltd¹
The Centre, First Floor, Birchwood Park,
Warrington, Cheshire WA3 6YN
United Kingdom

1.2.2. Producer or producers of the active substance

Confidential information, see Annex C.

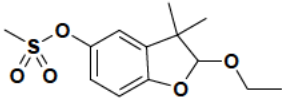
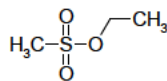
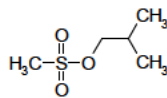
1.2.3. Information relating to the collective provision of dossiers

There are two notifiers for the renewal of Ethofumesate: Task Force Ethofumesate (representing Bayer CropScience and Adama Deutschland GmbH (former Feinchemie Schwebda GmbH)) and United Phosphorus Limited. As these companies were unable to come to an agreement for a joint submission, each submitted a separate dossier. Both dossiers were adjudged to be complete and have, therefore, been evaluated within this DRAR. The notifiers decided to share some of the studies; the appropriate letters of access have been submitted.

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	Ethofumesate (ISO 1750, published), no synonyms
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	(<i>RS</i>)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate
CA	2-ethoxy-2,3-dihydro-3,3-dimethyl-5-benzofuranyl methanesulfonate
1.3.3. Producer's development code number	Task force: <u>Bayer CropScience:</u> NC 8438 SN 49913 AE B049913 <u>Adama:</u> None allocated UPL: HBX06
1.3.4. CAS, EEC and CIPAC numbers	
CAS	26225-79-6
EEC	247-525-3
CIPAC	233
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	C ₁₃ H ₁₈ O ₅ S

¹ Throughout the DRAR UPL Europe Ltd is named UPL

Structural formula	
Molecular mass	286.3 u
1.3.6. Method of manufacture (synthesis pathway) of the active substance	CONFIDENTIAL information - data provided separately in Volume 4 for Bayer CropScience, Adama and UPL
1.3.7. Specification of purity of the active substance in g/kg	<p>Racemic mixture (1:1)</p> <p>Task force <u>Bayer CropScience</u> min. 960 g/kg (DAR 1998 reference source) min. 970 g/kg (Renewal)</p> <p><u>Adama:</u> min. 975 g/kg</p> <p>UPL min. 960 g/kg</p> <p>FAO 2007: min. 960 g/kg</p>
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. Additives	CONFIDENTIAL information - data provided separately in Volume 4 for Bayer CropScience, Adama and UPL
1.3.8.2. Significant impurities	CONFIDENTIAL information - data provided separately in Volume 4 for Bayer CropScience, Adama and UPL
1.3.8.3. Relevant impurities	<p>EMS Chemical name (IUPAC): methanesulfonic acid ethyl ester CAS number: 62-50-0 Molecular formula: C₃ H₈ O₃ S Structural formula:</p>  <p>Molecular mass: 124.16 u Max. content : 0.1 mg/kg</p> <p>IBMS Chemical name (IUPAC): ethyl, 1,1-dimethyl-2-[(methylsulfonyl)oxy]- CAS number: 16156-53-9 Molecular formula: C₅ H₁₂ O₃ S Structural formula:</p>  <p>Molecular mass: 152.21 u Max. content : 0.1 mg/kg</p>
1.3.9. Analytical profile of batches	CONFIDENTIAL information - data provided separately in Volume 4 for Bayer CropScience, Adama and UPL

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT**ETHOFUMESATE SC 500**

1.4.1. Applicant	Task Force Ethofumesate Bayer S.A.S Bayer CropScience 16 rue Jean-Marie Leclair CS 90106 69266 Lyon Cedex 09 France		
1.4.2. Producer of the plant protection product	Bayer S.A.S. Bayer CropScience 16, rue Jean-Marie Leclair CS 90106 69266 Lyon Cedex 09 France		
1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product	Trade names: Trammat 500, Norton 50 SC, Tender, Ethomat 500 (Ethofumesate SC 500). Current codes: Specification n° 102000002286 ; Material number UVP 05934729		
1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product			
1.4.4.1. Composition of the plant protection product		Ethofumesate 500 g/L	
1.4.4.2. Information on the active substances			Name/Code Number
		ISO common name	Ethofumesate
		CAS No.	26225-79-6
		CIPAC No.	233
		ELINCS / EINECS No.	247-525-3
		EU Index No.	607-314-00-2
		Salt, ester anion or cation present	no
1.4.4.3. Information on safeners, synergists and co-formulants		CONFIDENTIAL information - data provided separately in Volume 4.	
1.4.5. Type and code of the plant protection product		Suspension Concentrate (SC)	
1.4.6. Function		Herbicide	
1.4.7. Field of use envisaged		Sugar and fodder beet	
1.4.8. Effects on harmful organisms		Inhibitor of cell division	

ETHOFOL 500 SC

1.4.1. Applicant	United Phosphorus Limited The Centre, 1st Floor, Birchwood Park, Warrington, Cheshire WA3 6YN UK
1.4.2. Producer of the plant protection product	United Phosphorus Limited

	The Centre, 1st Floor, Birchwood Park, Warrington, Cheshire WA3 6YN UK	
1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product	Name: Ethofol 500 SC, other names: Ethofol SC, AD 496 (Ethofumesate 500 SC) Code number: HBX01	
1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product		
1.4.4.1. Composition of the plant protection product	Ethofumesate 500 g/L	
1.4.4.2. Information on the active substances	Type	Name/Code Number
	ISO common name	Ethofumesate
	CAS No	26225-79-6
	EC No	247 525-3
	CIPAC No	233
	Salt, ester anion or cation present	no
1.4.4.3. Information on safeners, synergists and co-formulants	CONFIDENTIAL information - data provided separately in Volume 4.	
1.4.5. Type and code of the plant protection product	Suspension Concentrate (SC)	
1.4.6. Function	Herbicide	
1.4.7. Field of use envisaged	Sugar and fodder beet	
1.4.8. Effects on harmful organisms	Inhibition of mitosis plus reduced photosynthesis and respiration	

1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.5.1. Details of representative uses

A) Task Force Ethofumesate

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc of a.i. g/kg (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	Kg a.s./hl min max (g/hl)	Water l/ha min max	kg a.s./ha min max (*) (g/ha)		
Sugar beet, fodder beet, red beet	North and South EU	Ethofumesate SC 500	F	Annual dicot weeds and annual grasses	SC	500 g/L	Overall spray	Post-emergence BBCH16 to BBCH18	1-3	5	0.05-1	100-400	0.2-1.0	*	The maximum amount of active substance must not exceed 1.0 kg/ha every 3 years. * PHI is covered by the normal vegetation period between last application and harvest

* For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).

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

(b) Outdoor or field use (F), greenhouse 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 N 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. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypry). **In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**

(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) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha)

(m) PHI - minimum pre-harvest interval

B) United Phosphorus Limited

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc of a.i. g/kg (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	Kg a.s./hl min max (g/hl)	Water l/ha min max	kg a.s./ha min max (*) (g/ha)		
Sugar beet, fodder beet	Northern, central, southern EU	Ethofol 500 SC	F	Annual weeds	SC	500 g/L	Overall spray	Pre-emergence	1	-		300-400	1		PHI covered by the vegetation period, max. 1 kg a.s./ha every three years
Sugar beet, fodder beet	Northern, central, southern EU	Ethofol 500 SC	F	Annual weeds	SC	500 g/L	Overall spray	Post-emergence until BBCH 18	6*	5		200-300	0.16*		PHI covered by the vegetation period, max. 1 kg a.s./ha every three years

*Splitting application with a maximum total rate of 1 kg a.s./ha per season. The maximum application rate per treatment is 0.33 kg a.s./ha. The critical GAP therefore is 3 applications of 0.33 kg a.s./ha. More applications (max.6) at a lower application rate are possible, but they do not represent the critical GAP.

- * For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).
- (a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)
- (b) Outdoor or field use (F), greenhouse 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 N 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. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxyppyr). **In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
- (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) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha)
- (m) PHI - minimum pre-harvest interval

1.5.2. Further information on representative uses

Please refer to section 1.5.1

1.5.3. Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

No other uses applied for to support the setting of MRLs beyond the representative uses.

1.5.4. Overview on authorisations in EU Member States

Both notifiers (Task Force Ethofumesate and UPL) provided the information on the authorized uses of their representative formulations in the EU Member States.

A) Task Force Ethofumesate

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
Austria	Full	2945	TRAMAT 500	SC	500	21/02/2008	31/12/2015	Sugarbeet Beet, fodder Beet, red (beetroot)
Belgium	Full	8090P/B	ETHOMAT 500	SC	500	04/07/2003	28/02/2014	Sugarbeet Beet, fodder Swiss chard (mangels) Beet, beta Chicory, witloof Chicory, wild Ryegrass, annual Ryegrass Tobacco, Virginian Bean, climbing French Bluegrass, Kentucky Spinach
		7110P/B	ETHOSIN FORTE SC	SC	500	29/07/1994	28/02/2014	Sugarbeet Beet, fodder Swiss chard (mangels) Chicory, witloof Chicory, wild Ryegrass, annual Ryegrass

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
		8595P/B	KEMIRON SC	SC	500	12/12/1995	02/02/2014	Tobacco, Virginian Bean, climbing French Bluegrass, Kentucky Spinach Sugarbeet Beet, fodder Swiss chard (mangels) Beet, beta Chicory, witloof Chicory, wild Ryegrass, annual Ryegrass Tobacco, Virginian Bean, climbing French Bluegrass, Kentucky Spinach Onion Sugarbeet Beet, fodder Beet, red (beetroot) Safflower Sunflower, common Pea, field Grass (seed production)
Czech Republic	Full	3679-5	STEMAT SUPER	SC	500	29/07/1998	31/07/2016	Beet, beta
Denmark	Full	18-451	ETHOSAN SC	SC	500	02/11/2005	31/07/2017	Beet, beta
		18-426	NORTRON SC	SC	500	27/01/1988	31/07/2017	Beet, beta
Finland	Full	1784	TRAMAT 500 SC	SC	500	31/10/1997	28/02/2014	Sugarbeet

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
France	Full	9000069	AGRIJET 500	SC	500	22/10/2008	31/12/2017	Burdock, great Warmwood, Roman Orache, garden Sugarbeet Beet, fodder Beet, red (beetroot) Beet, spinach Swiss chard (mangels) Safflower Pyrethrum Chicory, witloof Fescue, reed Fescue, meadow Fescue, red Common St. Johnswort Raygrass, Italian Ryegrass Chamomile, wild Balm, lemon Seed production minor crops Bean (Phaseolus vulgaris L.) Plantain, whorled Plantain, Spogel Bluegrass, Kentucky Valerian, common Lamb's lettuce
		9900406	BOXER SC 500	SC	500	03/12/1999	31/12/2017	Sugarbeet

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
		9900147	PATROL 500	SC	500	01/10/1999	31/12/2017	Beet, fodder Perfume, aromatic , medicinal, condiment plants Seed production minor crops Sugarbeet
		9600400	STEMAT 500 SC	SC	500	01/10/1996	31/12/2017	Beet, fodder Wormwood Sugarbeet Beet, fodder Safflower Fescue, reed St.Johnswort Ryegrass Balm, lemon
		9000069	TRAMAT F	SC	500	06/12/1990	31/12/2017	Valerian, common Burdock, great Warmwood, Roman Orache, garden Sugarbeet Beet, fodder Beet, red (beetroot) Beet, spinach Swiss chard (mangels) Safflower Pyrethrum Chicory, witloof Fescue, reed

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
Germany	Full	043078-00	TRAMAT 500	SC	500	12/01/1995	31/12/2015	Fescue, meadow
								Fescue, red
								Common St. Johnswort
								Raygrass, Italian
								Ryegrass
								Chamomile, wild
								Balm, lemon
								Seed production minor crops
								Bean (Phaseolus vulgaris L.)
								Plantain, whorled
								Plantain, Spogel
								Bluegrass, Kentucky
								Valerian, common
								Lamb's lettuce
								Sugarbeet
								Beet, fodder
								Foxglove, woolly
								St. Johnswort, golden
								Marjoram
								Chamomile, wild
								Parsley
								Narrow-leaved plantain
								Rosemary
								Spinach
								Savory, perennial
								Thyme, garden
Greece	Full	7154	NORTRON 50 SC	SC	500	04/02/1982	28/02/2013	Sugarbeet

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
Ireland	Full	7564	STEFES ETHO 50 SC	SC	500	31/03/2008	28/02/2013	Sugarbeet
								Beet, fodder
	Full	02658	NORTRON 50 SC	SC	500	30/01/2008	15/08/2016	Sugarbeet
								Beet, fodder
Italy	Full	6088	KEMIRON 500 SC	SC	500	12/09/1984	28/02/2013	Beet, red (beetroot)
								Swiss chard (mangels)
	Full	5804	TRAMAT FLO	SC	500	27/03/1984	28/02/2013	Sugarbeet
								Tobacco, Virginian
Latvia	Full	0013	NORTRON 50 SC	SC	500	10/08/1995	06/07/2015	Sugarbeet
								Beet, fodder
	Full	0036H/00	NORTRON	SC	500	21/03/2000	22/03/2017	Beet, red (beetroot)
								Sugarbeet
Luxembourg	Full	L01079-017	ETHOMAT 500	SC	500	01/07/2003	31/12/2014	Beet, fodder
								Beet, red (beetroot)
								Sugarbeet
								Beet, fodder
								Swiss chard (mangels)
								Beet, beta
								Chicory, witloof
								Chicory, coffee
								Ryegrass, annual
								Ryegrass
								Tobacco, Virginian

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
								Grassland
								Bean, climbing French
								Bluegrass, Kentucky
								Spinach
Montenegro	Full	6/0-03-0200/00004	NORTRON SUPER	SC	500	24/12/2000	24/12/2010	Sugarbeet
Netherlands	Full	12521 N-W3	TRAMAT 500	SC	500	27/02/2004	31/07/2016	Sugarbeet
								Beet, fodder
								Fescue, reed
								Fescue, red
								Ryegrass, annual
								Ryegrass, perennial
								Ryegrass
								Lawn, turf
								Grass (seed production)
Poland	Full	R-68/2011	KEMIRON	SC	500	05/03/2001	01/11/2021	Sugarbeet
			KONCENTRAT 500					Beet, fodder
			SC					Chrysanthemum indicum
Portugal	Full	AV 0092	TRAMAT 50	SC	500	30/11/1995	07/05/2018	Sugarbeet
Serbia	Temporary registration	321-01-410/2012-11	NORTRON SUPER	SC	500	24/12/2000	31/12/2013	Sugarbeet
Slovakia	Full	95-11-0222	STEMAT SUPER	SC	500	12/10/1995	31/07/2016	Onion
								Sugarbeet
								Beet, fodder
								Sunflower, common
								Pea
								Grass (seed production)
Spain	Full	19838	KEMITRAM 50 LA	SC	500	04/10/1994	31/07/2016	Sugarbeet

Country	Reg Status	Reg No	Tradename	Form. type	AS g/l	First Reg On	Reg Until	Crop/Uses
United Kingdom	Full	19932	TENDER	SC	500	22/02/1995	31/07/2016	Sugarbeet
								Tobacco, Virginian
								Sugarbeet
	Full	15310	TRAMAT 50 SC	SC	500	11/07/1980	31/07/2016	Beet, red (beetroot)
								Tobacco, Virginian
								Sugarbeet
	Full	19689	VERTICE	SC	500	01/09/1993	31/07/2016	Sugarbeet
								Beet, fodder
								Sugarbeet
	Full	12986	NORTRON FLO	SC	500	27/06/2008	17/07/2017	Tobacco, Virginian
								Sugarbeet
								Beet, fodder
								Beet, red (beetroot)
								Beet, red (beetroot)
								Swiss chard (mangels)

B) United Phosphorus Limited

Authorized uses (products, crops, target organisms, rates of application, timing of applications)	
Austria Ethofol 500 SC	Crops: sugar and fodder beets Targets: weeds Rates/timing: post-emergence, max. total dose 1 kg Ethofumesate/ha (only applied every 3 years), max. individual dose 0.66 L/ha, 3 applications with an interval of 5-14 days)
Belgium Ethofol 500 SC	Crops: beets Targets: annual monocotyledonous weeds, <i>Alopecurus myosuroides</i> , <i>Apera spica-venti</i> , cereals, <i>Poa annua</i> , <i>Stellaria media</i> Rates/timing: 1 pre-emergence application at 1.6-2.0 L/ha, max. 1 kg Ethofumesate/ha/3 years and max. 1 application/12 months. Crops: beets Targets: annual monocotyledonous weeds, annual dicotyledonous weeds, <i>Galium aparine</i> , <i>Mercurialis spp.</i> , <i>Persicaria spp.</i> , <i>Stellaria media</i> Rates/timing: post-emergence application at 0.4-0.8 L/ha (one application which may be fractionated), max. 1 kg Ethofumesate/ha/3 years and max. 1 application/12 months.
Denmark Ethofol 500 SC	Crops: beets Targets: annual weeds Rates/timing: max. 0.07 L/ha in tank mixture with a maximum of 71 g Ethofumesate/ha once every 3 years.
France Ethofol 500 SC	Crops: sugar and fodder beets Targets: weeds Rates/timing: max. total dose 1 L/ha (splitting application: 3-5 applications with interval of 7 days)
Lithuania Ethofol 500 SC	Crops: sugar and fodder beets Targets: annual dicotyledonous weeds and some annual monocotyledonous weeds. Rates/timing: max. total dose 1 kg Ethofumesate/ha, max. single dose 0.4 L/ha, 3 applications (in mixture).
Poland Ethofol 500 SC	Crops: sugar beets Targets: weeds Rates/timing: 1 pre-emergence application at 2.0 L/ha

United Kingdom Ethofol 500 SC	Crops: sugar and fodder beets Targets: broad-leaved weeds Rates/timing: max. total dose 2.0 L/ha, max. individual dose: 0.8 L/ha
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Ethofumesate is furthermore used in several further straight or mixed products. Furthermore, Ethofol 500 SC may also be used in grass crops in some countries.

Level 2

ETHOFUMESATE

2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

2.1. IDENTITY

All points of the data requirements regarding Section 1 have been addressed and the information supplied is acceptable. The technical specification for all producers (Bayer CropScience, Adama, and UPL) is provided in respective confidential parts (Volume 4). All active substances are produced at commercial stage and are considered equivalent to the reference source included in Annex I of the DAR 1998.

Beside the significant impurities which are confidential, two other impurities, EMS and IBMS (which are not present above 0.1 mg/kg in any source submitted for this DRAR), should be considered as relevant as they can occur in other productions (e.g. generic products) and have to be monitored.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

2.2.1. Summary of physical and chemical properties of the active substance

TaskForce Ethofumesate:

Technical grade ethofumesate are beige platelets with intensive not characteristic odor with low water solubility and low vapor pressure. The melting point of ethofumesate at atmosphere pressure is 70°C. It boiled under decomposition under atmospheric pressure and its boiling range is 305-320°C. It shows an endothermic effect in the temperature range of 65 to 90°C (melting point) and an exothermal decomposition in the temperature range 290-405°C with a mean energy of 375 J/g. The calculated Henry's law constant of ethofumesate is low, which indicates that the substance is not expected to evaporate from water to the atmosphere. The substance is not expected to dissociate in water in consideration of the molecular structure. The solubility in water is 50 mg/L at 25°C without pH effect. The partition coefficient, n-octanol/water is 2.7, which indicates that the substance will be slightly moderately absorbed to organic matter in soil and sediment. Ethofumesate is not a highly flammable solid in the sense of EC guideline A.10. No self-ignition temperature of ethofumesate was observed up to the maximum test temperature of 401°C. Ethofumesate has no explosive properties in the sense of EC guideline A.14 and no oxidizing properties in the sense of EC guideline A.17.

UPL:

Ethofumesate technical is a white crystalline powder which melts at about 70°C and decomposes above 220°C before reaching the boiling point. Additionally, it does not dissociate in water, has a limited to fair solubility in organic solvents and – most importantly – does not pose physical-chemical hazards, because Ethofumesate is neither flammable, nor auto-flammable, oxidising and explosive.

2.2.2. Summary of physical and chemical properties of the plant protection product

TaskForce Ethofumesate:

Ethofumesate SC 500 (specification number 102000002286) is a suspension liquid, light brown in colour. It has an aromatic, musty odour. The preparation has no explosive, auto-flammable and oxidising properties under normal condition of use. Its self-ignition is 501°C. Its pH is within the range which naturally occurs e.g. in soils.

Its persistent foaming has been tested and is in line with the requirements. The preparation is stable throughout the test period of 14 days at 54°C, 7 days at 0°C and 2 years at ambient temperature. The active substance is stable under storage conditions and does not decline to less than 95% of the content prior to the test. The content of relevant impurities in the preparation is less than 1mg/kg of Ethofumesate technical content. Its technical properties indicate that no particular problem have to be expected when it is used as recommended.

UPL:

Ethofol 500 SC is a creamy, off-white, flowable, homogeneous liquid, with a characteristic odour. The experiments revealed that it has no flash point between 25 and 100°C, however it developed a distinctive red glow at 384°C, the temperature regarded as self-ignition. The product is not explosive and oxidising, and has a neutral pH.

The storage stability at ambient temperature over a period of 2 years and after 12 weeks at 35°C showed good stability in terms of active substance content and product characteristics. Moreover, no issues have been detected while storing it at a temperature of 0°C for 7 days.

Results of the technical tests (spontaneity of dispersion, suspensibility, wet sieve test, pourability and persistent foaming) showed that Ethofol 500 SC is a preparation of a high technical quality which is compatible with several other products commonly used in plant protection.

2.3. DATA ON APPLICATION AND EFFICACY**2.3.1. Summary of effectiveness**

Ethofumesate has a useful weed spectrum that includes the control of *Alopecurus myosuroides*, *Setaria spp.*, *Poa annua*, *Amaranthus retroflexus* and *Mercurialis annua* and an outstanding control of *Stellaria media*. Beyond that, it was the first herbicide to give some control of the difficult weed *Galium aparine*.

In sugar beet it has primarily a marked effect on *Chenopodium album*, *Polygonum spp.*, and *Avena fatua* and strengthens the level of control achieved by other herbicides when used in coformulations or tank mixtures. The weed spectrum of Ethofumesate is complementary with several currently marketed products. Hence, its weakness on *Matricaria spp* and *Sinapis spp* can be overcome by the addition of chloridazon, lenacil or phenmedipham, whereas Ethofumesate provides improved control of grass weeds, *Galium aparine*, *Chenopodium*, *Polygonum*. The main value of Ethofumesate is its residual action in the soil that helps to provide a control of the succeeding flushes of weed germination without requiring too many repeated applications; Compared to other pre-emergence herbicides, its efficacy is less bond to soil moisture. Indeed, the use of Ethofumesate in pre-emergence provides some flexibility to position following applications in post emergence. This property has been the basis for the low-dose/ low volume techniques that have been developed in some European countries like UK (so called FAR technology). Another approach has been, in parallel, to develop a series of various 2- and 3-way herbicide coformulations requiring only one-third of the active substance per hectare that used to be previously involved in beet production during the last 20 years. These reduced rates, have resulted into improved crop safety and yield enabling much earlier herbicides applications for a better control of weeds. Beyond the biological efficacy, these new products containing Ethofumesate offer substantial benefits in

terms of reduction of operator exposure and environmental pollution as well as a less constraints on the choice of following crops.

Within the turf and grassland markets, Ethofumesate offers a fairly unique mode of action and selectivity which can provide control of important weeds in establishing grass crops such as *Poa annua*, *Alopecurus myosuroides* and *Stellaria media* within preferred grass species such as *Lolium* and *Agrostis* and even *Festuca*. It can also assist in rejuvenating established grass swards, so avoiding the need for expensive ploughing up and re-seeding and the consequential losses of production in the interim.

2.3.2. Summary of information on the development of resistance

There is no evidence of the development of resistance to ethofumesate by grass weeds or broad-leaved weeds in over 30 years of use.

To avoid the development of resistance, repeated use of high rates is not recommended and the implementation of low-dose sequential applications, usually in co-formulations or tank-mixtures with other herbicides, has allowed the rates of use to be reduced progressively over the years. Since the active substance is generally used in mixtures and/or sequences with other herbicides in any one season, and due to crop rotational practices, it would not usually be re-applied on an annual basis to the same field.

2.3.3. Summary of adverse effects on treated crops

In normal conditions, means moisture and temperature compatible with sugar beet growth, Ethofumesate is safe for sugar beet. It can be applied both in pre-emergence as well as in post-emergence of the crop. In case of application in difficult growing conditions, such as frost or high temperature some symptoms can be visible such as leaf deformation and stunting but the recovery is excellent so that in the end no impact on the final yield can be recorded. Attention should be paid on peculiar soils salty or with extreme pH.

2.3.4. Summary of observations on other undesirable or unintended side-effects

Years of commercial uses have demonstrated that Ethofumesate when used according to the label recommendation is particularly safe and does not induce any particular undesirable effects such as carry over on the following crops. This explains why this active is a corner stone in sugar beet weeding.

2.4. FURTHER INFORMATION

2.4.1. Summary of methods and precautions concerning handling, storage, transport or fire

For information on active substance please see Volume 3CA, B4.

For information on representative formulations please see Volume 3CP, B4 for Ethofol 500 SC and Ethofumesate SC 500, respectively.

2.4.2. Summary of procedures for destruction or decontamination

For information on active substance please see Volume 3CA, B4.

For information on representative formulations please see Volume 3CP, B4 for Ethofol 500 SC and Ethofumesate SC 500, respectively.

2.4.3. Summary of emergency measures in case of an accident

For information on active substance please see Volume 3CA, B4.

For information on representative formulations please see Volume 3CP, B4 for Ethofol 500 SC and Ethofumesate SC 500, respectively.

2.5. METHODS OF ANALYSIS

2.5.1. Methods used for the generation of pre-authorisation data

Adequate methods are available for the analysis of the technical compound. Some amendments are required for the risk assessment analysis if considered necessary for the relevant sections.

2.5.2. Methods for post control and monitoring purposes

Adequate methods are available to monitor the respective current residue definition in plant material, soil, drinking water, surface water and air.

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

2.6.1. Summary of absorption, distribution and excretion in mammals

Absorption and Excretion

In rats ethofumesate was rapidly absorbed and rapidly eliminated after both, single and multiple oral administration of low (1 mg/kg body weight) and high dose (100 mg/kg body weight), mainly via urine (66 – 92% of administered radioactivity). Following intravenous administration of the low dose, radioactivity was rapidly excreted mainly via urine, but with a proportion also being excreted via faeces, indicating (although not measured) some biliary excretion (16% in males and 6% in females in faeces). Oral administration of the high dose appeared to saturate the absorption, since the faecal excretion of radioactivity was higher (containing a large portion of parent compound) than after the administration of low dose. The parent compound was not found in urine samples (< 1%).

Toxicokinetic parameters like C_{max}, T_{max} and plasma T_{1/2} of ethofumesate were not reported in any of the studies provided. For the metabolite ethofumesate-carboxylic acid, the calculated half-life in plasma was given as approximately 1.6 hours.

Based on the results of studies in rats after single oral low dose administration the oral absorption ranged from 66 to 90%. These values are based on renal excretion only since no biliary excretion was measured. However, after intravenous application of single low dose, radioactivity was found in faeces indicating entero-hepatic excretion. In one study with repeated low dose application excretion via urine was shown to be 81.3 – 91.7%. The later study was regarded appropriate to conclude that the oral absorption of ethofumesate is > 80% and that no adjustment of AOEL is necessary.

Distribution

After administration of single oral low dose to rats the highest radioactivity concentration in most tissues was reached 1 hour post-dosing, except in fat where the highest amount was 4 h post-dosing. Distribution of radioactivity into tissues was very even with highest amount of radioactivity detected in liver, kidneys and fat. 5 days after administration of single oral low and high dose, as well as repeated dose, the proportion of dose remaining in tissues was very low. There was no evidence of accumulation.

Metabolism

In rat urine, the major metabolite was ethofumesate-carboxylic acid (93-97% of urine radioactivity). The minor metabolites were identified as ethofumesate-lactone (1-4%) and ethofumesate-2-hydroxy (up to 2%). In faeces of high dose groups, the main component (25-48% of faeces radioactivity) was parent compound.

Only few metabolic transformations were observed in rats. The pattern of metabolites indicated that the desalkylation of ethofumesate can be regarded as the most important step in the metabolic pathway in the rat because all identified metabolites were found without the ethyl substituent.

Two studies (no OECD Guideline available, considered only as supplementary information) were submitted for renewal to evaluate if there is any unique human metabolite, not present in rat metabolism. While ethofumesate was totally transformed towards ethofumesate-carboxylic acid in rat microsomes, the human microsomal incubations produced beside ethofumesate-carboxylic acid two further main metabolites (ethofumesate-2-hydroxy and ethofumesate-lactone). However, these metabolites were identified in rat in vivo metabolism studies as well.

It is concluded that the observed differences in metabolism between the rat and human liver microsome incubations are presumably due to dissimilarities of phase I biotransformation reactions in the tested species and that shorter incubation periods with rat liver microsomes would lead to a more similar metabolic pattern.

Both metabolites ethofumesate-carboxylic acid and ethofumesate-lactone (as part of the residue definition for food of plant and animal origin) were identified in rat metabolism studies, ethofumesate-carboxylic acid being the major component in urine. Since ethofumesate-carboxylic acid is the last compound in the metabolic degradation pathway of ethofumesate in rats and built by degradation of ethofumesate-lactone (ring-opening), it is considered that ethofumesate-lactone also contributes to the toxicological profile of ethofumesate observed in the toxicity studies.

2.6.2. Summary of acute toxicity

A series of studies were carried out to investigate the acute effects of ethofumesate, administered by oral, dermal and inhalation route and its potential for skin and eye irritancy and skin sensitisation. According to the new data requirements, also the phototoxic potential of ethofumesate was investigated.

Ethofumesate has very low oral and dermal acute toxicity and both LD₅₀ values were estimated far above the guidance value for classification (> 2000 mg/kg bw). Regarding acute inhalation toxicity, it appears that the efficiency for generating a respirable test atmosphere with ethofumesate is very low. In the only study where the MMAD was below 4 µm, the maximum attainable concentration was 0.16 mg/L. The acute inhalation LC₅₀ was > 0.16 mg/L. Ethofumesate is neither skin nor eye irritant. In none of the skin sensitisation studies skin reaction upon dermal challenge was observed. In addition, in one M&K test no positive control was reported while in the Buehler test the number of treated animals was too low. However, as a weight of evidence, ethofumesate is not considered to be skin sensitiser.

At the time it is concluded that based on the negative results of 3T3 NRU-PT, which is currently the only listed test for addressing phototoxicity (Commission Communications 2013/C 95/01), ethofumesate is not considered to be phototoxic.

No non-lethal effects in acute oral toxicity studies were observed which would warrant the classification as STOT SE (specific target organ toxicity - single exposure) for ethofumesate.

Overview of results of the acute toxicity studies, studies for skin and eye irritation, skin sensitisation and phototoxicity

Study type, species	Purity %	Result (LD ₅₀ , LC ₅₀)	References
Acute oral toxicity studies			
<i>Rat</i>	-*	> 2000 mg/kg bw	██████, 1992
	98	> 7500 mg/kg bw	██████, 1991
	-*	> 5000 mg/kg bw	██████, 1988
	-*	> 8000 mg/kg bw	██████, 1988
<i>Mouse</i>	-*	> 5000 mg/kg bw	██████, 1992
	98	> 7500 mg/kg bw	██████, 1991
	-*	> 8000 mg/kg bw	██████, 1988
Acute dermal toxicity studies			
<i>Rat</i>	-*	> 2000 mg/kg bw	██████, 1992
	-*	> 2000 mg/kg bw	██████, 1988
	98	> 5000 mg/kg bw	██████, 1991
<i>Rabbit</i>	97.8	> 20050 mg/kg bw	██████, 1979
Acute inhalation toxicity studies			
<i>Rat</i>	98	> 0.16 mg/l	██████, 1991
	97	> 0.3 mg/l	██████ <i>et al.</i> , 1989
	-*	> 3.97 mg/l	██████ <i>et al.</i> , 1988
	-*	-	██████ <i>et al.</i> , 1986
Skin irritation			
<i>Rabbit</i>	-*	no irritation	██████, 1992
	98	no irritation	██████, 1991
	98	no irritation	██████, 1991
Eye irritation			
<i>Rabbit</i>	-*	no irritation	██████, 1993
	98	no irritation	██████, 1991
	98	mild irritation	██████, 1991
Skin sensitisation			
<i>Guinea pigs (GPMT)</i>	-*	no sensitisation	██████, 1989
<i>Guinea pigs (Buehler)</i>	98	no sensitisation	██████, 1991
<i>Guinea pigs (GPMT)</i>	96.8	no sensitisation	██████ <i>et al.</i> , 1984

Phototoxicity			
Neutral red (NR) test with BALB/c 3T3 cells	99.8	Not phototoxic	Heppenheimer, 2012

*) purity grade not given / not reported

2.6.3. Summary of short-term toxicity

A series of studies were carried out to investigate the effects of orally administered ethofumesate in rats (three 28 days studies, four 90 days studies), mice (one 90-day study) and dogs (one 28 days and one 90 days study) following repeated exposure via the oral route over subchronic periods. In addition, the effects after repeated exposure via the dermal route were also investigated in the rabbit (one 21 days study).

The lowest NOAEL in 28 days oral studies was 200 mg/kg bw/d in male and female rats. In 90-days oral studies the lowest NOAEL was 3000 ppm (190 mg/kg bw/d in males and 230 mg/kg bw/d in females); however, huge dose-spacing in the studies should be considered.

The main effects after oral exposure in rats and dogs were effects on body weight gain and on weight of liver and kidney, sometimes accompanied with histopathological findings in these organs or changes in chemical chemistry parameters at highest tested doses. Whilst the rats and the dogs showed effects at comparable doses the mice seem to be less susceptible to ethofumesate. Ethofumesate did not cause any effects on rabbits in the short term dermal toxicity study at the highest tested dose of 1000 mg/kg bw/d.

No effects on rats in 28 days oral toxicity studies were observed below the value of 300 mg/kg bw/d which is considered as guidance value for potential classification of substances as STOT-RE 2 (specific target organ toxicity – repeated exposure). Similarly, no effects on rats and mice were observed in 90 days oral toxicity studies below the value of 100 mg/kg bw/d which is considered as guidance value for potential classification of substances as STOT-RE 2 after 90 days exposure period. According to Regulation (EC) No 1272/2008 no guidance values are set for effects observed in dog studies, however, ethofumesate did not cause any effects in dogs which would trigger classification as STOT-RE at tested doses.

Overview of results of the short-term studies

Study	Purity (%)	Dose levels	NOAEL mg/kg bw/day	Effects at LOAEL	References
28 days studies – oral route					
Rats					
Feeding study in Sprague Dawley rats	—*	10000, 20000 and 30000 ppm ethofumesate (approximately 1000, 2000 and 3000 mg/kg bw/d)	2000 (males and females)	↓ b.w. gain	██████ <i>et al.</i> , 1989
Feeding study in CD rats	98.9	300, 3000 and 30000 ppm 30.5, 297, 3081 mg/kg bw/d (males) 33.1, 320, 3219 mg/kg bw/d (females)	297 (males) 320 (females)	↓ b.w. gain ↑ liver weight	██████ <i>et al.</i> , 1988
Feeding study in Wistar rats	98	200, 2000, and 20000 ppm (approximately 20, 200 and 2000 mg/kg)	200	↑ liver weight ↑ kidney weight	██████ <i>et al.</i> , 1991

Study	Purity (%)	Dose levels	NOAEL mg/kg bw/day	Effects at LOAEL	References
		bw/d)		↓ neutrophiles ↓ Na ⁺ and Ca ²⁺	
Dogs					
Feeding study in Beagle dogs	~*	1: 10-2000 mg/kg/ bw/d 2: 500, 1000, 2000 mg/kg bw/d	1000	↑ spleen weight ↑ glomerular vacuolar degeneration in kidneys	██████ <i>et al.</i> , 1994
90 days studies – oral route					
Rats					
Feeding study in Sprague Dawley rats	99.5	0, 1000, 5000, 20000 ppm 78, 350 and 1449 mg/kg bw/d (males) 88, 410 and 1651 mg/kg bw/d (females)	350 (males) 410 (females)	↓ b.w. and b.w gain ↑ liver weight ↑ kidney weight	██████ <i>et al.</i> , 1989
Feeding study in Wistar rats	98	0, 200, 2000, and 20000 ppm 14, 140 and 1400 mg/kg bw/d (males) 18, 160 and 2000 mg/kg bw/d (females)	1400 (males) 2000 (females)	-	██████, 1992
Feeding study in Sprague Dawley rats	98.9	300, 3000 and 30000 ppm 18.2, 190 and 1900 mg/kg bw/d (males) 23.4, 230 and 2309 mg/kg bw/d (females)	190 (males) 230 (females)	↓ body weight gain (f) ↑ liver weight (m/f) ↑ kidney weight (m/f) ↑ uterus weight ↑ spleen weight (m) Histological findings (kidney, liver) (m)	██████ <i>et al.</i> , 1989
Feeding study in Sprague Dawley rats	~*	500, 1000, 1500, and 3000 ppm 50, 100, 150 and 300 mg/kg bw/d	> 300	-	██████, 1990
Mice					
Feeding study in CD-1 mice	97	300, 3000 and 10000 ppm 45, 450 and 1500 mg/kg bw/d	> 1500	-	██████, 1990
Dogs					
Feeding study in Beagle dogs	98.6	250, 750 and 1500 mg/kg bw/d	250	↑ alkaline	██████ <i>et al.</i> , 1994

Study	Purity (%)	Dose levels	NOAEL mg/kg bw/day	Effects at LOAEL	References
				phosphatase ↑liver weight	
21 day study – dermal route					
Dermal study in NZW rabbits	98.3	100, 300 or 1000 mg/kg bw/d	> 1000	-	██████ <i>et al.</i> , 1991

*) purity grade not given / not reported

2.6.4. Summary of genotoxicity

Ethofumesate was tested in many genotoxicity and mutagenicity tests *in vitro* and *in vivo*. There was no indication of gene mutation either in the presence or absence of metabolic activation in both the bacterial reverse mutation (five AMES tests) and mammalian gene mutation tests (one test on HGPRT locus of L5178Y mouse lymphoma cells, one test on HGPRT locus of CHO cells). A negative response for chromosomal aberrations was observed *in vitro* (two studies with human lymphocytes, one study on CHO cells). The *in vitro* test for DNA damage and repair (UDS) was negative.

In mouse micronucleus test *in vivo* two negative and one positive result were observed. No confounders for one positive MN test could be identified. Two tests for chromosomal aberrations *in vivo* (one on rat and one on mice) were negative. In the dominant lethal test on Wistar rats no effects on fertility indices were observed.

Based on the entire comprehensive data package it is concluded that ethofumesate has no genotoxic potential *in vitro* and *in vivo*.

No OECD Guideline is currently available for testing photomutagenicity and no study was provided by the notifiers. The waiving of the study is considered acceptable as long as no test methods or guidance documents are published in form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02.

Overview of results of the genotoxicity studies

Test	Purity (%)	Concentration	Result	References
<i>In vitro</i>				
Bacterial assays for gene mutation				
<i>S. typhimurium</i> (TA 1535, TA 1537, TA 98 TA 100), <i>E. coli</i> (CM 881 and CM 891)	97.2	15-5000 µg/plate (±S9)	negative	Gant, 1994
<i>S. typhimurium</i> (TA 1535, TA 1537, TA 1538, TA 98, TA 100)	98-99	62-5000 µg/plate (±S9)	negative	Wilmer, 1987
<i>S. typhimurium</i> (TA 1535, TA 1537, TA 1538, TA 98, TA 100)	98	100-10000 µg/plate (±S9)	negative	Suresh, 1993
<i>S. typhimurium</i> (TA 1535, TA 1537, TA 98, TA 100, TA102)	96.3	3-5000 µg/plate (±S9)	negative	Sokolowski, 2013
<i>S. typhimurium</i> (TA 1535, TA 1537, TA 1538, TA 98, TA 100)	-*	8-5000 µg/plate (±S9)	negative	Thompson, 1992

Test	Purity (%)	Concentration	Result	References
Gene mutation in mammalian cells				
L5178Y mouse lymphoma cells, HGPRT locus	96.2	7.9-250 µg/ml (±S9)	negative	██████ 1986
Chinese hamster ovary cells, HGPRT locus	98-99	50-250 µg/ml (±S9)	negative	██████ 1986
Clastogenicity in mammalian cells				
Human lymphocytes	96.2	11, 55, 110 µg/ml (±S9)	negative	██████ 1986
Chinese hamster ovary cells	98-99	1.3-175 µg/ml (±S9)	negative	██████, 1987
Human lymphocytes	-*	39-5000 µg/ml (±S9)	negative	██████ 1992
DNA damage and repair				
Unscheduled DNA synthesis in primary rat hepatocytes	96.2	1.56-200 µg /ml	negative	██████ <i>et al.</i> , 1988
In vivo somatic cells				
Mouse micronucleous assay	96.3	8100 mg/kg bw	negative	██████ <i>et al.</i> , 1985
Mouse micronucleous assay	97	500-5000 ml/kg bw	negative	██████ <i>et al.</i> , 1992
Mouse micronucleous assay	98	40-4000 mg/kg bw	positive	██████ 1993
Chromosome aberration in mice	98	40-4000 mg/kg bw	negative	██████ 1994
Chromosome aberration in rats	-*	3000 mg/kg bw	negative	██████, 1992
In vivo germ cells				
Dominant lethal assay	98	200-5000 mg/kg bw	negative	██████, 1992

*) purity grade not given / not reported

2.6.5. Summary of long-term toxicity and carcinogenicity

A series of chronic and carcinogenicity studies were carried out to investigate the effects of orally administered ethofumesate in rats, mice, hamsters and dogs following repeated exposure via the oral route.

The main effects after oral exposure were effects on body weight gain and on weight of liver, sometimes accompanied with histopathological findings in liver or changes in clinical chemistry parameters. The lowest NOAEL in rodents (rats, mice) was 1000 ppm.

No effects on rodents were observed below the values of 25 mg/kg bw/d (chronic studies) and 12.5 mg/kg bw/d (carcinogenicity studies) which are considered as guidance values for potential classification of substances as STOT-RE 2 (specific target organ toxicity – repeated exposure). According to Regulation (EC) No 1272/2008 no guidance values are set for effects observed in dog studies, however, ethofumesate did not cause any effects in dogs which would trigger classification as STOT-RE at tested doses. No treatment related neoplastic findings were observed in any of the studies. Therefore, ethofumesate is considered not to be potentially carcinogenic

substance.

Overview of results of genotoxicity studies

Study	Purity (%)	Dose levels	NOAEL mg/kg bw/day	Effects at LOAEL	References
Rats					
1 year feeding study in Sprague Dawley rats	At least 97	0, 2000, 7000 20000 ppm 135, 470 and 1338 mg/kg bw/d (males) 164, 630 and 1849 mg/kg bw/d (females)	2000 ppm 135 (males) 164 (females)	↓ bw gain (females) ↑ histological changes in the liver (males and females)	██████ et al., 1990
2 years feeding study in Sprague Dawley rats	At least 97	0, 2000, 7000 20000 ppm 115, 392 and 1161 mg/kg bw/d (males) 134, 529 and 1595 mg/kg bw/d (females)	2000 ppm 115 (males) 134 (females)	↑ histological changes in the liver (males and females) No carcinogenicity	██████ et al., 1991
2 years feeding study in Wistar rats	92.5	0, 8, 40, 200, 1000 or 5000 ppm 0.3, 1.5, 7.4, 37.6 and 192.4 mg/kg bw/d (males) 0.4, 1.7, 8.7, 44.5 and 235.7 mg/kg bw/d (females)	1000 ppm 37.6 (males) 44.5 (females)	↑ mortality ↓ bw gain (females) ↑ liver weight (males) No carcinogenicity	██████ 1976
2 years feeding study in Wistar rats	98.0	0, 100, 1000 or 10000 ppm 6.9, 69 and 715 mg/kg bw/d (males) 9.8, 101 and 1169 mg/kg bw/d (females)	1000 ppm 101 mg/kg bw/d (females)	↓ bw gain (females) No carcinogenicity	██████ 1995
Mice					
80 weeks feeding study in CrI:CD-1(ICR) BR mice	97.0	0, 1000, 3000 or 10000 ppm 161, 477 and 1601 mg/kg bw/d (males) 204, 644 and 2145 mg/kg bw/d (females)	3000 ppm 644 mg/kg bw/d (females)	↑ liver weight (females) No carcinogenicity	██████ et al., 1992
Hamster					
19 – 22 months feeding study in of Syrian hamsters (BIO 15.16)	96.8	0, 80, 400 and 2000 ppm 5.4, 26 and 130 mg/kg bw/d (males) 5.6, 28 and 143 mg/kg bw/d (females)	400 ppm 28 mg/kg bw/d	↑ liver weight (females) No carcinogenicity	██████ 1980
Dogs					
104 weeks feeding study in Beagle dogs	96.6 – 98.0	0, 800, 4000 and 20000 ppm 25, 118 and 632 mg/kg	4000 ppm 118 (males) 109 (females)	↑ liver weight (males and females) ↑ ALT (males and	██████ 1980

Study	Purity (%)	Dose levels	NOAEL mg/kg bw/day	Effects LOAEL at	References
		bw/d (males) 24, 109 and 619 mg/kg bw/d (females)		females)	

2.6.6. Summary of reproductive toxicity

Multigeneration studies

Four multigeneration studies (one of them range finding study) were carried out to investigate the effects of orally administered ethofumesate in rats.

The main effects on parental animals after oral exposure were effects on body weight gain and inconsistent effects on organ weights not accompanied by any histopathological findings. The lowest parental NOAEL was 1000 ppm.

The effects on reproduction in studies with ethofumesate were minimal and limited to effects on mean litter size and pre-implantation loss in animals of highest tested doses; however these effects were not confirmed in all generations within one study. The lowest reproductive NOAEL was 1000 ppm.

The effects on offspring at very high tested doses (30000 ppm) were effects on pups survival and bad clinical condition of pups. In studies with moderate tested doses the effects were limited to decreased body weight gain and incomplete ossification. Effects like reduced live birth index, reduced 21 day survival index and reduced number of male pups were not confirmed in following generation. The lowest foetal NOAEL was 1000 ppm.

Based on huge dose spacing in the studies the NOAELs are considered to be even higher than 1000 ppm.

No effects on rodents were observed which are considered relevant for potential classification of substance as reproductive toxicant. Therefore, ethofumesate is considered not to be potentially reprotoxic substance with regard to effects observed in multigeneration studies.

Overview of results of multigeneration studies

Study	Purity %	Dose levels	NOAEL	Effects observed at the LOAEL	References
Dietary rat reproductive performance Dose ranging study	-*	0, 3750, 7500, 15000 and 30000/50000 ppm	<u>Parents:</u> 30000/50000 ppm (males) 15000 ppm (females)	Males: no effects Females: mortality ↓ body weight gain clinical signs	██████ P., 1989
			<u>Offspring:</u> 15000 ppm	adverse effect on pups survival bad clinical condition	
			<u>Reproduction:</u> 15000 ppm	reduced mating performance	
Dietary two generation rat reproduction toxicity study	97	0, 3000, 10000 and 30000 ppm	<u>Parents:</u> 10000 ppm (males) (approx. 700	Males: ↓ body weight gain ↑ relative testes weight	██████ P., 1990

Study	Purity %	Dose levels	NOAEL	Effects observed at the LOAEL	References
			mg/kg bw) 3000 ppm (females) (approx. 200 mg/kg bw)	Females: ↓ body weight gain ↓ absolute and relative ovaries weight	
			<u>Offspring:</u> 3000 ppm (approx. 200 mg/kg bw)	↓ body weight gain Retardation of pups development	
			<u>Reproduction:</u> 10000 ppm (approx. 640 mg/kg bw)	↓ litter size	
Dietary three generation rat reproduction toxicity study	97.8	0, 300, 1000 and 5000 ppm 16, 78 and 397 mg/kg bw/d (males) 18, 88 and 454 mg/kg bw/d (females)	<u>Parents:</u> 1000 ppm (males) (78 mg/kg bw/d)	Males: ↑ absolute weight of lungs, liver, kidneys ↓ relative weight of thyroid and testes	[REDACTED] [REDACTED] [REDACTED] [REDACTED] 1980
			1000 ppm (females) (88 mg/kg bw/d)	Females: ↓ body weight gain ↑ absolute and relative uterus weight ↓ absolute and relative thyroid weight	
			<u>Offspring:</u> 1000 ppm (78 mg/kg bw/d)	↑ number of foetuses with incomplete ossification of cranial bones	
			<u>Reproduction:</u> 5000 ppm (397 mg/kg bw/d)	No effects at 5000 ppm	
Dietary two generation rat reproduction toxicity study	98	0, 100, 1000 and 10000 ppm 5.9, 60.9 and 654 mg/kg bw/d (males) 8.3, 90.7 and 939.7 mg/kg bw/d (females)	<u>Parents:</u> 1000 ppm (males) (60.9 mg/kg bw/d) 1000 ppm (females) (90.7 mg/kg bw/d)	↓ body weight gain (males and females)	[REDACTED] 1993
			<u>Offspring:</u> 1000 ppm (60.9 mg/kg)	↓ live birth index in P ₀ ↓ 21 day survival index in P ₀	

Study	Purity %	Dose levels	NOAEL	Effects observed at the LOAEL	References
			bw/d)	↓ number of male pups in P ₀	
			<u>Reproduction:</u> 1000 ppm (60.9 mg/kg bw/d)	↑ pre-implantation loss in P ₀ generation ↓ mean litter size in P ₀	

*) purity grade not given / not reported

Developmental toxicity studies

In total, six main teratology studies were performed on ethofumesate, three on rat and three on rabbit. One of the studies on each species was conducted as a limit dose test. The results from three studies on Sprague-Dawley rats did not show any toxic effects on dams and offspring and the NOAEL from these studies are the same as the highest doses, 1000 and 4000 mg/kg bw, respectively.

Regarding rabbit developmental studies (all conducted on New Zealand white rabbits), the lowest NOAEL for dams is assumed at 600 mg/kg bw/d (the two NOAELs of 300 mg/kg bw/d are considered too conservative based on dose spacing in the studies), based on mortalities and reduced body weight and food intake at doses of approximately 1500 mg/kg bw/d. For offspring, the lowest NOAEL was approximately 1500 mg/kg bw/d (300, 1000 and 1200 mg/kg bw/d from other studies are considered too conservative based on dose spacing in these studies) based on post-implantation loss at 2000 mg/kg bw/d. Neither in rat nor in rabbit teratogenic effects were observed.

Overview of results of developmental studies

Study	Purity %	Dose levels	NOAEL	Effects observed at the LOAEL	References
Rat					
Developmental range finding study in Sprague-Dawley rats	> 97	0, 300, 1000 or 2000 mg/kg bw/d	<u>Maternal:</u> 2000 mg/kg bw/d	No effects at highest dose tested	[REDACTED], L. 1991
			<u>Offspring:</u> 2000 mg/kg bw/d	No effects at highest dose tested	
Developmental study in Sprague-Dawley rats	> 97	0, 1000, 2000 and 4000 mg/kg bw/d	<u>Maternal:</u> 4000 mg/kg bw/d	No effects at highest dose tested	[REDACTED] L. 1991
			<u>Offspring:</u> 4000 mg/kg bw/d	No effects at highest dose tested	
Developmental study in Sprague-Dawley	97	0, 10, 100 and 1000 mg/kg bw/d	<u>Maternal:</u> 1000 mg/kg bw/d	No effects at highest dose tested	[REDACTED] R., 1991

Study	Purity %	Dose levels	NOAEL	Effects observed at the LOAEL	References
rats			<u>Offspring</u> : 1000 mg/kg bw/d	No effects at highest dose tested	
Developmental study inWistar rats (limit test)	98	0 and 1000 mg/kg bw/d	<u>Maternal</u> : 1000 mg/kg bw/d	No effects at highest dose tested	██████, T. P., 1991
			<u>Offspring</u> : 1000 mg/kg bw/d	No effects at highest dose tested	
Rabbit					
Developmental range finding study in New Zealand white rabbits	-*	0, 300, 1500 and 2000 mg/kg bw/d	<u>Maternal</u> : 300 mg/kg bw/d	↑ mortality ↓ bw gain ↓ food intake	██████ L., 1991
			<u>Offspring</u> : 1500 mg/kg bw/d	↑ post-implantation loss	
Developmental study in New Zealand white rabbits	> 97	0, 300, 600 and 1200 mg/kg bw/d	<u>Maternal</u> : 600 mg/kg bw/d	↓ bw gain ↓ food intake	██████, L., 1991
			<u>Offspring</u> : 1200 mg/kg bw/d	No effects at highest dose tested	
Developmental study in New Zealand white rabbits (limit test)	98	0 and 1000 mg/kg bw/d	<u>Maternal</u> : 1000 mg/kg bw/d	No effects at highest dose tested	██████ T. P., 1993
			<u>Offspring</u> : 1000 mg/kg bw/d	No effects at highest dose tested ↑ incidences of dilated right heart ventricle	
Developmental study in New Zealand white rabbits	-*	0, 30, 300 and 3000 mg/kg bw/d	<u>Maternal</u> : 300 mg/kg bw/d	↑ mortality ↑ absorptions ↓ bw gain	████████████████████ ████████████████████ ████████████████████ 1986
			<u>Offspring</u> : 300 mg/kg bw/d	↑ post-implantation loss ↓ mean foetal weight ↑ incomplete ossifications	

*) purity grade not given / not reported

2.6.7. Summary of neurotoxicity

There are no indications from the existing data package that ethofumesate has effects on the nervous system. Therefore, no specific neurotoxicity studies are required.

2.6.8. Summary of further toxicological studies on the active substance

There are no indications from the existing data package that ethofumesate has effects on the endocrine system. No recognised endocrine disrupting effects were observed *in vivo* and it is considered unlikely that any mechanistic study would add any relevant information. Therefore, no specific studies on endocrine disruption are required. Ethofumesate also does not fulfil the criteria for endocrine disruptors stated in the Regulation (EC) 1107/2009.

Ethofumesate did not cause any mortalities applied by intraperitoneal route and the LD50 was > 2000 mg/kg bw.

Study type, species	Purity %	Result (LD ₅₀ , LC ₅₀)	References
Acute intraperitoneal			
Rat	-	> 2000 mg/kg bw	1993
	-	> 2000 mg/kg bw	1993

2.6.9. Summary of toxicological data on impurities and metabolites

No studies on metabolites were evaluated in the original DAR (1998) and this was also not considered necessary. For purpose of renewal the notifier TaskForce provided a package of genotoxicity studies *in vitro* with the assumed groundwater metabolite called “BCS - CU88901” (the sodium salt of metabolite NC 20645 – carboxylic acid).

There was no indication of gene mutation either in the presence or absence of metabolic activation in both the bacterial reverse mutation (AMES test) and mammalian gene mutation tests (V79/HPRT). A negative response for chromosomal aberrations was also observed *in vitro* (Chinese hamster V79 cells).

Based on the FOCUS calculations there are no groundwater metabolites of ethofumesate exceeding the trigger of 0.1 µg/l. Therefore, according to *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*, no relevance assessment and no studies on genotoxicity of sodium salt of metabolite NC 20645 are considered necessary.

2.6.10. Summary of medical data and information

The conducted literature search did not result in any relevant information addressing either poisoning incidents or other human data with ethofumesate, or any information on potential neurotoxic effects of this substance.

The reported cases from human data included single cases of headache and drowsiness however they were attributed to solvent in the formulation. There have been no epidemiological studies conducted in groups exposed to ethofumesate.

2.6.11. Toxicological end point for assessment of risk following long-term dietary exposure - ADI

For the first approval of ethofumesate the ADI was set at 0.07 mg/kg bw/d based on the NOAEL of 100 ppm (6.9 mg/kg bw/d) in the 2 years feeding study in rats () based on reduced body weight gain at 1000 ppm. After re-evaluation of this study, the RMS is of the opinion that the NOAEL of the study should be 1000 ppm (69 mg/kg bw/d in males and 101 mg/kg bw/d in females), since at 1000 ppm no consistent effects on body weight gain

above 10% reduction were observed. Also no other effects, except increased relative ovarian weight (+32%) without any histopathological findings, were observed at 1000 ppm in this study.

The new derived NOAEL of 1000 ppm in the DRAR (2014) from study of ████████ 1995, corresponding to 69 mg/kg bw/d in male and 101 mg/kg bw/d in female rats is still the lowest NOAEL of the valid long-term studies in rats, mice and dogs. Therefore, the RMS proposes to base the ADI on the female rat NOAEL of 101 mg/kg bw/d (consistent effects on body weight gain were observed only in females from month 12 to 24), which would result in a new ADI of 1 mg/kg bw/d. The new ADI is supported by findings in several multigeneration, chronic and carcinogenicity studies in rats, mice and dogs where the lowest NOAEL was never below 1000 ppm.

2.6.12. Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

For the first approval of ethofumesate no ARfD was derived since it was not considered necessary. After the re-assessment of the original DAR, and based on all available information, the RMS for the renewal of ethofumesate follows this opinion. No acute effects (haematotoxicity, immunotoxicity, neurotoxicity, liver and kidney toxicity, developmental effects²) were observed in acute/sub-chronic/multigeneration and developmental studies which can be likely considered to present an acute hazard at relevant doses.

2.6.13. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL

For the first approval of ethofumesate the AOEL was set at 2.5 mg/kg bw/d based on the NOAEL of 250 mg/kg bw/d in the 90 days dog study (██████ et al., 1994). This conclusion is also supported for the renewal of the ethofumesate (2014). The NOAELs observed in rat short term studies were partially slightly lower but the dose spacing in rat studies was essentially larger. Therefore, it is considered appropriate to assume 250 mg/kg bw/d as the lowest NOAEL in the short term studies especially since no differences in target organs were observed between rats and dogs.

2.6.14. Summary of product exposure and risk assessment

2.6.14.1. Ethofumesate 500 SC (Task Force)

Ethofumesate 500 SC is a herbicidal product, applied in sugar beet, fodder beet and red beet at a maximum application rate of 1.0 kg a.s/ha.

The estimated operator exposure does not exceed the AOEL of 2.5 mg/kg bw/d, resulting in 11.3% of AOEL in UK POEM and 1.5% in German Model without personal protective equipment. Detailed calculations are presented in Volume 3 CP, B.6.4.1.

² Guidance on setting of acute reference dose (ARfD) for pesticides. Food and Chemical Toxicology 43 (2005), 1569 – 1593.

Bystander and resident exposure for adults and children are low, resulting in maximum of 0.18% of AOEL for adult resident and in 0.36% of AOEL for children residents (Martin et al., 2008). Detailed calculations are presented in Volume 3 CP, B.6.4.2.

The worker exposure for scouting activities (EUROPOEM II) is 1% of the AOEL without personal protective equipment. Detailed calculations are presented in Volume 3 CP, B.6.4.3.

An *in vitro* dermal absorption study using rat and human skin was submitted. The study was performed with the comparable formulation Nortron SC 500 (for comparisons of formulations please see Volume 4). The derived values were 0.4 % for the concentrate, 2% for 10 g/L dilution and 8% for 0.5 g/L dilution. The tested dilutions cover the complete range of in-field dilutions and are considered appropriate for the risk assessment.

2.6.14.2. Ethofol 500 SC (UPL)

Ethofol 500 SC is a herbicidal product, applied in sugar and fodder beet at a maximum application rate of 1.0 kg a.s./ha.

The estimated operator exposure does not exceed the AOEL of 2.5 mg/kg bw/d, resulting in 58.6% of AOEL in UK POEM and 5.5% in German Model without personal protective equipment. Detailed calculations are presented in Volume 3 CP, B.6.4.1.

Bystander and resident exposure for adults and children are low, resulting in maximum of 0.21% of AOEL for adult resident and in 0.4% of AOEL for children residents (Martin et al., 2008). Detailed calculations are presented in Volume 3 CP, B.6.4.2.

The worker exposure for scouting activities (EUROPOEM II) is 2% of the AOEL without personal protective equipment. Detailed calculations are presented in Volume 3 CP, B.6.4.3.

An *in vitro* dermal absorption study with Ethofol 500 SC using human skin was submitted. The derived values were 3 % for the concentrate and 20% for 0.17 g/L dilution. The tested dilution is more diluted than any in-field dilution and is considered appropriate for the risk assessment.

2.7. RESIDUE

2.7.1. Summary of storage stability of residues

2.7.1.1. Plant matrices

The storage stability of ethofumesate was evaluated in the first EU approval process. Ethofumesate was found to be stable up to 2 years.

Additional studies were submitted to address the storage stability of the metabolites NC 20645 and NC 20645 conjugates.

After a deep freezer storage period at -18°C of up to 24 months (729 days), the recovery rates for metabolite NC 20645 in stored samples of sugar beet leaves, sugar beet roots (i.e. high water and high starch containing commodities), ranged between 72-102% for sugar beet roots and between 71-110% for sugar beet leaves.

Procedural recoveries for metabolite NC 20645 determined from freshly fortified samples ranged between 73-109% (sugar beet roots) and between 75-106% (sugar beet leaves).

Altogether, the study results show a good stability of NC 20645 in sugar beet (roots and tops with leaves) for up to 24 months when stored frozen at -18°C.

2.7.1.2. Animal matrices

The deep freezer storage stability at -21°C of ethofumesate, NC 8493, NC 9607 (determined as NC 20645) and NC 20645 was investigated in bovine muscle, liver, kidney, fat and milk for a period of about 6 months. According the study design reported in the interim report, the storage stability study is still ongoing up to 24 months.

In liver and kidney, metabolite NC 8493 was found to readily convert to NC 9607 or NC 20645, both of which are detected and measured as NC 20645. Since the common moiety NC 20645 is included in the residue definition, stability for NC 8493 in liver is addressed by measuring NC 20645 in the stored liver samples, if existent. Although residues of NC 8493 were analysed as NC 20645 degradation to recovery results slightly below 70 % (68 %) were observed in kidney. The metabolite NC 8493 is not part of the residue definition in animal matrices. The storage stability results on NC 8493 have not impact to the validity of the animal feeding study.

There was no evidence of any continued degradation of these compounds in muscle, fat and milk, when stored deep-frozen over the tested period of 6 months.

The results validate the residue values reported in the cattle feeding study with respect to storage stability of samples frozen prior to analysis. In case of kidney the metabolite NC 8493 was converted to NC 20645 and led to recovery values of 68%.

2.7.2. Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

2.7.2.1. Plant matrices

Metabolism of ethofumesate was investigated in root and tuber vegetables (sugar beet and onions), cereals (ryegrass) and leafy crops (tobacco) following application of [¹⁴C-benzene]- or [¹⁴C-methylsulfonyl]-ethofumesate. Application was conducted either as a pre-emergent or a post-emergent spray. The application rate in the sugar beet studies ranged between approx. 1.3-2.0 kg a.s./ha and between 2.0 and 2.1 kg a.s./ha in the other crops. Comparison of pre-and post-emergent treatment revealed that ethofumesate is taken-up via roots and leaves. The metabolism in the plants is independent from the route of uptake.

The studies on sugar beet and on ryegrass show a conclusive picture on the metabolic behaviour of ethofumesate. Two additional studies on sugar beet and the studies on onion and tobacco were conducted before the implementation of GLP certificates and are therefore considered as supportive data only. However, these studies are in very good agreement with the GLP studies and confirm the results of these studies. Nevertheless, the metabolism study representing the cereal group was conducted on ryegrass and therefore no information on cereal grains is available from this study.

The major metabolic pathway for ethofumesate in plants was identified as follows:

- cleavage of the ethoxy side chain, with hydroxylation at the 2 position to give metabolite NC 8493 (ethofumesate-2-hydroxy = 2,3-dihydro-2-hydroxy-3,3-dimethylbenzofuran-5-yl methanesulfonate).
- This metabolite can either undergo conjugation to give polar metabolites or oxidation to the lactone NC 9607 (ethofumesate-lactone = 2,3-dihydro-3,3-dimethyl-2-oxobenzofuran-5-yl methanesulfonate).
- The lactone ring opens to the carboxylic acid NC 20645 (ethofumesate-carboxylic acid = 2-(2-hydroxy-5-methanesulfoxyphenyl)-2-methyl propionic acid) which can also undergo conjugation to give polar metabolites.

The lactone NC 9607 and the carboxy analogue NC 20645 are inter-convertible and depending on the ambient conditions, either one or the other metabolite will predominate. Under acidic conditions, metabolite NC 20645 is converted to metabolite NC 9607 by an intramolecular ring closure. Vigorous acidic treatment (3 M or 6 M HCl) of the extracts or the polar fraction itself showed that the polar compounds were acid-labile and were transformed to discrete known moieties (NC 8493 and NC 9607).

The amount of metabolite NC 8493 decreased with time, indicating a further degradation/conjugation.

Cleavage of the molecule under release of methanesulphonic acid was excluded in two sugar beet studies. The extraction and analysis processes were validated beforehand with a radiolabelled reference compound (^{14}C -MSA). Recoveries of MSA were above 97% and confirmed that the compound would be detected, if present.

The extractability of radioactive residues was high in sugar beet shoots and ryegrass; surface wash and conventional solvent extraction released between 86.4-99.9% of the total radioactive residue. If an additional exhaustive extraction step with hydrochloric acid was applied, the extraction efficiency was always >90%. Exhaustive extraction released generally the known moieties NC 8493 and NC 9607. The extractability in roots was generally lower due to the high sugar and starch content of the tissue. Nevertheless, 75.8-93.7% of the radioactivity was released by conventional solvent extraction.

Very low residues were detected in mature roots of sugar beets after application of 1.3-2.0 kg a.s./ha. The total radioactive residue ranged between <0.01-0.03 mg/kg at harvest when considering all studies conducted. Due to the low residue level at maturity, identification of the residues was only possible in a root sample of the overdose experiment collected 10 days after treatment. The nature of the residues in this sample was intensively examined - before and after hydrolysis of the extracts - and it was clearly shown that the residues in roots are identical with those of shoots. No exhaustive extraction of the bound residues was conducted, however on the basis of all other experiments; it can be assumed that additional amounts of the known metabolites NC 8493 and NC 9607 could be released. Analysis of mature roots of the one overdose experiment revealed the presence of parent ethofumesate and high amounts of the polar fraction, indicating the presence of the polar conjugates of metabolites NC 20645 and NC 8493 besides the parent compound.

Overall, the plant metabolism studies showed that all crops under investigation followed the same metabolic pathway. Final residues were always dominated by a polar fraction. The polar fraction was acid labile and could be converted to the common moiety NC 9607 (major amount) and metabolite NC 8493 by vigorous treatment with hydrochloric acid. Since ethofumesate itself is also acid-labile under these vigorous conditions decomposition to NC 8493 is possible. Since major amounts of metabolite NC 8493 were only detected in intermediate growth stages it was considered as not necessary to include this metabolite in the residue definition for mature crops, as well as its conjugate which was always a minor metabolite. Thus with parent compound

ethofumesate and the common moiety NC 9607 two adequate compounds are found which describe the relevant residue of ethofumesate in mature crops. Since the common moiety NC 9607 and NC 20645 are interconvertible, the pH value in the final extract determines which of the compounds the analytical target is.

In conclusion, all plant metabolism studies have shown that there is extensive metabolism of ethofumesate in plants from both pre- and post-emergence uses. No significant quantities of uncharacterised or unidentified metabolites have been found. Although the route of metabolism of ethofumesate in all crops studied is very similar it has to be pointed out that the definition of residue can be established only for root crops because the metabolism study on ryegrass did not provide any information about the metabolic behaviour in cereal grains.

The metabolism of ethofumesate in plants is very similar to that observed in livestock and rats.

2.7.2.2. Animal matrices

Ruminants:

A lactating dairy cow was orally dosed twice daily for four consecutive days with [^{14}C -benzene]-ethofumesate. The mean daily dose was 2.94 g (equivalent to 5.0 mg/kg body weight). This dose rate was equivalent to an exposure of 274 mg/kg in the diet.

Identification of the metabolites was carried out in milk and edible tissues containing residues higher than 0.01 mg/kg, namely in liver, kidney, psoas muscle, omental fat, subcutaneous fat and renal fat.

Following dosing of ^{14}C -ethofumesate for four consecutive days, residues were detectable in all edible tissues between 0.033 and 1.863 mg/kg. The highest residue was detected in kidney as metabolising organ; the lowest residues were detected in muscle. In most tissues the major component was identified as unchanged parent compound followed by metabolites NC 20645, NC 8493 and NC 9607 which were detected in smaller quantities. In the kidney, the major metabolite identified was the highly water soluble NC 20645 which was readily excreted. Residue levels in milk reached a maximum of 0.134 mg/kg at 32 hours post-administration of the initial dose. The major compound identified was parent compound followed by metabolite NC 20645. Other metabolites identified were NC 8493 and NC 9607 each accounted for less than 10% of the residue.

Excretion via urine was the major elimination pathway for ethofumesate. Transfer of radioactive residues in edible tissues and milk was low.

Poultry:

In egg yolks and whites, residue levels of ethofumesate were detectable 24 hours after the initial dose administration (0.8 mg/kg bw) with residue levels in egg yolks continuing to rise to reach a plateau by day 8 of dosing at a concentration of 0.019 ± 0.001 mg/kg. The residue level in egg whites was an order of magnitude lower, with a maximum concentration of 0.002 mg/kg seen on day 5 of dosing. In undeveloped eggs (eggs of ovary and oviduct), the mean concentration of ethofumesate-derived residue was 0.024 ± 0.003 mg/kg.

Residue levels of ethofumesate and/or its metabolites in the edible tissues of the hen were low, with the highest concentration seen in the liver (0.095 ± 0.034 mg/kg). Residues in skin and abdominal fat were lower at 0.020 ± 0.006 mg/kg and 0.019 ± 0.003 mg/kg respectively. Subcutaneous fat levels were also low, at 0.016 ± 0.003

mg/kg. Skeletal muscle levels were the lowest of the edible tissues at 0.007 ± 0.005 mg/kg. Thus transfer of radioactivity into edible tissues is very low.

Following administration of the first dose of ethofumesate, elimination of the radioactivity was rapid with >80% of the recovered radioactivity excreted within twenty-four hours.

Ethofumesate was present in all tissues and was the major residue identified in egg yolk, fat and skin. NC 20645 (the carboxy analogue of NC 9607) was the major residue identified in the muscle and liver and was also present in the skin and egg yolk. NC 9607 (the lactone) was present in all tissues, the hydroxy derivative NC 8493 was present at low levels in the muscle. A polar fraction (probably containing conjugates of the known metabolites) and some unidentified metabolites were also determined at very low levels.

Based on the metabolites identified in edible animal tissues, the following metabolic routes were deduced:

- Cleavage of the ethoxy side chain, with hydroxylation at the 2 position, to give NC 8493.
- NC 8493 can undergo oxidation to the lactone NC 9607.
- The lactone ring of NC 9607 can open to form the carboxy analogue NC 20645.

The metabolic patterns identified for cows were consistent with the rat metabolism and no metabolism study on pig is required.

2.7.3. Definition of the residue

2.7.3.1. *Plants matrices*

Residue definition for risk assessment and enforcement

The metabolism of ethofumesate was investigated in sugar beet, onion, tobacco and ryegrass for foliar and/or soil applications and in confined rotational crops (cabbage, radish, and wheat) after application of ethofumesate onto bare soil and cultivating of succeeding crops at three plant-back intervals. Whereas the metabolism studies on onion and tobacco were considered as supporting information only.

The metabolism in ryegrass does not cover in full extent the metabolism in cereal crop as no information is available for cereal grains.

The metabolism in rotational crops was shown to be similar to the metabolism in primary crops. In rotational field trials, the highest total residues of ethofumesate were found in rotational root crops where detectable residues were only found as ethofumesate; residues of the common moiety NC 9607 were always below the LOQ of 0.01 mg/kg in carrot roots and leaves. In green material taken earlier in the rotation, ethofumesate residues were below the LOQ of 0.01 mg/kg and the residues of the common moiety NC 9607 ranged from <0.01-0.02 mg/kg.

Based on the metabolism studies on primary and succeeding crops the following residue definition is proposed:

Ethofumesate (sum of ethofumesate and its metabolites NC 9607³ and 20645⁴ (free and conjugated))

³ NC 9607: AE C509607: 2,3-dihydro-3,3-dimethyl-2-oxo-benzofuran-5-yl methane sulphonate

⁴ NC 20645: AE C520645: 2-(2-hydroxy-5-methanesulfoxyphenyl)-2-methyl propionic acid

It has to be mentioned that the current residue definition for risk assessment and enforcement is only applicable if a hydrolysis step is included in the residue method in order to cleave the major plant metabolite (conjugate of NC 20645) to its exocon and convert it to NC 9607 as analytical target. Since NC 9607 and NC 20645 (the ring open form of NC 9607) are interconvertible depending on the ambient conditions.

Generally the relevant ethofumesate metabolites are detected after conversion to a common moiety which can be either NC 9607 or NC 20645.

2.7.3.2. Animal matrices

Residue definition for risk assessment and enforcement

The metabolism of ethofumesate was investigated in cows and laying hens.

The main compounds identified in cow and hens are ethofumesate and the metabolites NC 20645 (NC 8493 and NC 9607 which were detected in smaller quantities).

Based on these metabolism studies the following residue definition is proposed:

Ethofumesate (sum of ethofumesate and its metabolites NC 9607 and 20645)

2.7.4. Summary of residue trials in plants and identification of critical GAP

Sugar beet is assigned as major crop in Northern and Southern Europe. Hence, eight residue trials are required for each geographical growing zone.

Between 1972 and 2012, numerous residue trials were conducted to support the presented “representative use” (pre-emergence and post-emergence use) of ethofumesate in *Beta vulgaris*, the trials were conducted in different growing areas in the northern and southern European residue region. The vegetation period in sugar and fodder beet ranges between 5 and 9 months and the studies indicate that the variation within the vegetation period is much higher than the time period between pre- and post-emergent treatment. Final residues were always at the same level.

However, the post emergence use (treatment around BBCH 14-18) with single application rate at approximately 1 kg a.s./ha was considered as the worst-case use regarding the magnitude of residues in mature sugar-, and fodder beet roots.

In the northern European climatic zone 34 post-emergence trials and for the southern European region 11 post-emergence trials were used for MRL calculation. The results are summarised in the following table.

Table 2.7-1 Summary on data from the supervised residue trials northern and southern Europe

Crop	Region	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs	HR (mg/kg)	STMR (mg/kg)
Beetroots		extrapolation from sugar beets		
sugar beet leaves Chard/beet leaves	NEU	8x<0.02, 11x<0.06, 0.06, 0.07, 9x<0.1, <0.12, 0.18	0.18	0.06
	SEU	6x<0.02, 0.04, 0.06, 0.14	0.14	0.02
sugar beet roots	NEU	8x<0.02, 14x<0.06, 0.09, 11x<0.1	0.1	0.06
	SEU	8x<0.02, 3x<0.06	0.06	0.02

The results of all trials conducted in the southern European residue region demonstrate that:

- The data set is considered as sufficient to cover the intended use.
- Following one early application (either pre- or early post emergence), residue levels of “total ethofumesate” in sugar beets declined significantly with time and residue levels were at or below the limit of quantification in mature sugar beet roots and leaves at harvest.

2.7.5. Summary of feeding studies in poultry, ruminants, pigs and fish

According to the data requirements for the dossiers to be submitted for the approval of active substances (Regulation (EU) 283/2013), feeding studies shall be provided where metabolism studies indicate that residues at levels of above 0.01 mg/kg may occur in edible animal tissue, milk, eggs or fish, taking into account the residue levels in potential feeding stuffs, obtained at the 1x dose rate, calculated on the dry weight basis.

According to the OECD guidance document on residues in livestock published on July 10th 2013 (ENV/JM/MONO(2013)8), fodder beets, sugar beet tops, dried pulp of beets, ensiled pulp of beets and molasses are the beet matrices fed to livestock. In addition, rotational crops, planted directly after crop failure (within 30 days after treatment of the failed beet crop) can show small ethofumesate related residues. These rotational crops can also contribute to the animal diet. The dietary burdens were calculated for different groups of livestock using the summarised residue values and the OECD calculator.

Table 2.7-2 Ethofumesate related residues in animal feed items

Crop	Residue [mg/kg]	
	HR	STMR
Primary crops		
Sugar / fodder beet root	0.12	0.06
Sugar / fodder beet tops	0.14	0.06
Processed commodities		
Sugar beet, dried pulp		0.35 ¹
Sugar beet, ensiled pulp		0.06 ¹
molasses		1.27
Rotational crops		
Cereal, forage	0.03	0.03
Root crops, root	0.05	0.04

1 value estimated based on the residue in sugar beet root (dry matter (DM) = 15) and the DM of 88 for dried pulp and DM of 15 for ensiled pulp

2 median processing factor of 12.7 for molasses was applied (cf. CA 6.5.3)

Table 2.7-3 Anticipated dietary burden for ethofumesate residues in livestock based on EU residue data (OECD calculator)

	Dietary burden (mg/kg bw/day)	Dietary burden (mg/kg DM)
Cattle		
Beef	0.012	0.5
Dairy cattle	0.022	0.6
Sheep		
Ram/Ewe	0.015	0.4
Lamb	0.019	0.4
Swine		
Breeding	0.007	0.3
Finishing	0.007	0.2
Poultry		
Broiler	0.003	0.04
Layer	0.005	0.08
Turkey	0.003	0.04

1 value estimated based on the residue in sugar beet root (dry matter (DM) = 15) and the DM of 88 for dried pulp and DM of 15 for ensiled pulp

2 median processing factor of 12.7 for molasses was applied (please refer to B 7.5.3)

Table 2.7-4 Transfer factors determined in the cow metabolism study (cf. KCA 6.2.3 /03) (dietary burden in the metabolism study = 274 mg/kg dry feed, equivalent to ~ 5 mg/kg bw)

Sample	Transfer of total residue
Milk (Σ 8-95 h samples)	0.002
Subcutaneous fat	0.002
Omental fat	0.002
Renal fat	0.002
Kidney	0.007
Hind quarters muscle	<0.001
Psoas muscle	<0.001
Loin muscle	<0.001
Heart muscle	<0.001
Liver	0.002

Table 2.7-5 Transfer factors determined in the poultry metabolism study (cf. KCA 6.2.2 /02) (dietary burden in the metabolism study = 11 mg/kg dry feed, equivalent to ~ 0.8 mg/kg bw)

Sample	Transfer of total residues
Egg yolk (steady state: day 8)	0.002
Egg white (steady state: day 6)	<0.001
Muscle	<0.001
Skin	0.002
Fat, abdominal	0.002
Fat, subcutaneous	0.001
Liver	0.008

Considering the transfer factors for the total radioactive residue in an animal matrix, as estimated in the livestock metabolism studies, and the corresponding maximum dietary burden of the animal, it becomes obvious that the residues in all animal matrices will not exceed 0.01 mg/kg and therefore no feeding studies have to be conducted, neither in ruminants nor in poultry.

In the scope of the original Annex I inclusion process, a feeding study in poultry and two feeding studies in lactating cow were evaluated. All feeding studies were conducted in the US and did not completely follow the EU guidelines, however confirmed the low transfer of the ethofumesate related residues in edible matrices.

2.7.6. Summary of effects of processing

The nature of ethofumesate residues under conditions representative for processing was investigated for pasteurisation, baking, brewing, boiling, sterilisation and industrial extraction and purification, due to the use of Ethofumesate in sugar beets. The additional hydrolysis experiment was performed at pH 11, 90°C for 30 min. This test is a simulation of the carbonation process used in the sugar production. The radiolabelled test compound [phenyl-UL-¹⁴C]-ethofumesate was used for the hydrolysis investigations.

One concentration (approx. 1.0 mg/L) of the analyte was prepared in sterilized buffered drinking water and incubated under three representative sets of hydrolysis conditions:

Pasteurisation:	90°C at pH 4 for 20 min
Baking, brewing, boiling:	100°C at pH 5 for 60 min
Sterilisation:	120°C at pH 6 for 20 min
Industrial extraction and purification:	90°C at pH 11 for 30 min

At test termination, the material balances in all tests were in the range of 99.9 to 100.6% of the applied radioactivity, indicating that no radioactivity and no volatile degradation products dissipated from the test system.

The test compound amounted to $\geq 97.9\%$ in all test solutions before and after hydrolysis. No significant hydrolysis products of ethofumesate ($\leq 2.1\%$) were detected above an estimated LOD of 0.7% of the total radioactivity.

Several processing studies were submitted and evaluated during the Annex I inclusion process of ethofumesate. These studies demonstrated that ethofumesate related residues were never present in refined sugar indicating that probable residues in the raw agricultural commodity are efficiently eliminated during processing. A concentration of the residue was detected in molasses (maximum and median processing factor was 24 and 12.7, respectively) and in thick juice (maximum and median processing factor was 6.5 and 4.7, respectively). The studies were considered acceptable. Therefore, no additional data was considered necessary.

2.7.7. Summary of residues in rotational crops

Metabolism in rotational crop

During first approval process, the metabolism of ethofumesate in rotational crops was evaluated in wheat, radish and cabbage following soil application of [14 C-benzene]-ethofumesate.

Parent ethofumesate was the major compound in radish roots, but a minor compound in shoots and in the aerial plant parts of all other crops. The second major compound was metabolite NC 20645, free or in conjugated form. This metabolite and its conjugate were also the main residue in all aerial plant parts, followed by metabolite NC 9607. Metabolite NC 8493 was also detected as free metabolite or as conjugate.

Hence, the plant-back interval of crop failure (plant-back interval of 30 days) was not covered by the initially provided study, a new study on the metabolism in rotational crops was submitted which covers the plant-back interval of 30 days.

This report corroborates the results of the confined rotational crop study which have already been reviewed on EU level. Based on the results of this study it can be concluded that the nature of residues in rotational crops is similar to that in primary crops and the proposed residue definition for plants for monitoring and risk assessment is therefore still applicable (the sum of ethofumesate, 2-keto-ethofumesate (NC 9607), open-ring-2-keto-ethofumesate (NC 20645) and its conjugate).

Based on the metabolites identified in following crops, the following metabolic routes were deduced:

- Cleavage of the ethoxy side chain, with hydroxylation at the 2 position, to give NC 8493.
- NC 8493 can either undergo conjugation to give polar metabolites, or oxidation to the lactone NC 9607.
- The lactone ring of NC 9607 opens to the carboxy analogue NC 20645 which can also undergo conjugation to give polar metabolites.

Thus, the metabolic routes detected are in line with those observed in primary crops. On the basis of these results it can be concluded that the metabolism of [14 C]-ethofumesate in confined rotational crops is well understood and follows the same metabolic path as primary crops:

Magnitude of residues in rotational crops

Several field rotational crop studies – either as “multi-crop” study (containing data for two rotations with three crop groups: leafy, root, and cereal crops) or as “limited” study (containing data for one rotation with one crop) were conducted during the first approval process. The studies were conducted with exaggerated field rates, either in Europe or the US. Since none of the study was conducted with the current application rate of 1.0 kg as./ha, an additional field rotational crop study was submitted in addition.

In the framework of this evaluation process 2 additional studies were submitted.

In the **first study** four rotational crop field trials were conducted in Europe (2 each in the northern and southern residue regions). Ethofumesate was applied once either to bare soil or to a target crop (sugar beet) at an active substance rate of 1.0 kg/ha, the target crop was then harvested, and crops representing 3 different botanical groups (roots, leafy veg., cereals) were planted on the plots at 3 intervals thereafter.

Residues of ethofumesate in all rotational crops were only detected in the first rotation, i.e. grown after a plant-back interval (PBI) of 25-33 days.

The highest total residues of ethofumesate in rotational root crops (immature carrot roots sampled approx. 14 days prior to the mature crop) ranged from <0.02-0.05 mg/kg. Residues in the mature roots ranged from <0.02-0.04 mg/kg. Residues were also determined in the leaves and ranged from <0.02-0.04 mg/kg, independent if harvested from the immature or the mature crop. Detectable residues were only found as ethofumesate; residues of the common moiety NC 9607 were always below the LOQ of 0.01 mg/kg in carrot roots and leaves.

In lettuce, cereals grain and straw no residues of ethofumesate and NC 9607 above the LOQ of 0.01 mg/kg were detected.

In green material taken earlier in the rotation, ethofumesate residues were below the LOQ of 0.01 mg/kg and the residues of the common moiety NC 9607 ranged from <0.01-0.02 mg/kg. Thus the total residue ranged from <0.02-0.03 mg/kg in green material of the first rotation.

In the **second study** two field rotation trials were carried out. At both trials, ethofumesate was applied once at 1 kg as/ha to sugar beets. The application was carried out at a BBCH 14-16 except for the plot with a plant-back interval of 30-31 days and the rotation with spring barley. Three different crop groups (leafy vegetables, root vegetables and cereal) were planted at three different plant back intervals (30-41 days, 90-176 days and 335 days). No residues of Ethofumesate and the sum of its metabolites NC9607 + NC20645 above the LOQ (0.01 mg/kg for each analyte for root and leafy vegetable matrices and 0.05 mg/kg for each analyte for cereal matrices) were found in any of the control and treated specimens.

No residues of Ethofumesate and its metabolites included in the proposed residue definition need to be expected in rotational crops after application of Ethofumesate according to the intended GAP.

Summarising the above, it can be concluded that ethofumesate related residues are only expected at or slightly above the LOQ. The highest residues in mature crops were detected as ethofumesate in root crops up to 0.03 mg/kg where ethofumesate was applied as pre-emergence application on bare soil.

2.7.8. Summary of other studies

Open literature search

The search of open literature resulted in a publication about stereoselective degradation of ethofumesate in turfgrass and soil (Wang, P. et al.; 2005; M-458577-01-1; published). This supplementary information has no impact on the data presented in this section since degradation of ethofumesate in plants was found to be fast and resulted in non-chiral metabolites.

Preferential degradation of the (-)-enantiomer was observed in both grass species and in one of the tested soils. In grass the enantiomeric ratio (ER) amounted to about 3 and in the soil to a value of ER = 1.65, resulting in residues enriched with (+)-enantiomer. The stereoselective degradation in one of the tested soils led to a significant difference in the half-lives of the two enantiomers. No stereoselective degradation was observed in the other two soils under investigation.

However, the preferential degradation of the (-)-enantiomer, as observed in both grass species and in one soil, has no influence on the dietary exposure of consumers. Plant metabolism studies have shown a fast degradation of ethofumesate to non-chiral metabolites. .

Livestock studies have also shown that a transfer of ethofumesate related residues (taken up by feedstuffs) in edible matrices of the animals is negligible and will not lead to any residues above 0.01 mg/kg in edible matrices of livestock.

Effect on the residue level in pollen and bee products

Sugar beets, fodder beets and beetroots are harvested before flowering and are therefore no feeding crops for bees. In addition, no internationally agreed guidelines are available for conducting a study addressing this data requirement.

Nevertheless, a statement was provided within this dossier which outlines the situation for honeybees in detail.

The risk for honeybees to get in contact with contaminated nectar and pollen is negligible as sugar and fodder beets do not build flowers within the first year. Sugar and fodder beets are harvested by the end of the first year. In the rare case that shoots with flowers are produced in the first year or beets are flowering in the second year (if beets are grown for seed production) no risk for honeybees is expected as beet flowers are wind pollinated. Sugar and fodder beet flowers are not mentioned in any standard or handbook on honey bee foraging plants

The beet structure does not allow formation of water reservoirs in leaf axils. The risk for honeybees to get in contact with Ethofumesate residues in guttation fluid being present at the leaf edges as guttation droplets at sugar and fodder beets after ethofumesate treatment is very low as well. Hence, beets are very unattractive water sources for honeybees.

2.7.9. Estimation of the potential and actual exposure through diet and other sources

The assessment of the chronic uptake of ethofumesate residues with food was calculated based on the proposed MRLs values and the Acceptable Daily Intake (ADI) of 1mg/kg bw/day, which was established based on the two-year rat study and a 100x uncertainty factor. Acute exposure calculations were not carried out because an ARfD was not deemed necessary for this active substance.

2.7.9.1. Acceptable Daily Intake (ADI) and Dietary Exposure Calculation

The chronic exposure assessment was calculated using the proposed MRL values for beetroots (0.2 mg/kg), chards/beet leaves (0.3 mg/kg) and sugar beets (0.2 mg/kg).

The highest ADI exhaustion with respect to the representative uses was calculated for the UK toddler resulting in 0.46 % of the ADI

Table 2.7-6 Ethofumesate – Summary of the TMDI calculation with respect to the representative uses (EFSA PRIMo model rev. 2.0)

TMDI (% ADI)	Diet	Highest contributor to the diet (% ADI)	Commodity
0.46	UK Toddler	0.457	Sugar beet (root)
0.20	UK Infant	0.202	Sugar beet (root)
0.08	UK Adult	0.080	Sugar beet (root)
0.08	UK vegetarian	0.076	Sugar beet (root)
0.03	WHO Cluster diet B	0.014	Beetroot

The estimated Theoretical Maximum Daily Intakes (TMDI) for ethofumesate with regard to the representative uses is below 1% of the ADI for all consumer groups. Thus no chronic consumer risk could be identified.

2.7.10. Proposed MRLs and compliance with existing MRLs

EU MRLs for ethofumesate are listed in Annex II and Part B of Annex III to regulation (EC) No 396/2005 as published in Commission Regulation (EU) 524/2011, dated May 26, 2011. The published MRLs for the representative uses are listed in the table below.

Table 2.7-7 EU MRLs for ethofumesate as published in EU Regulation 524/2011

Code number	Groups and examples of individual products to which the MRLs apply (a)	Ethofumesate#
200000	2. VEGETABLES FRESH OR FROZEN	
210000	(i) Root and tuber vegetables	
213010	Beetroot	0.1
252000	(b) Spinach & similar (leaves)	
252030	Beet leaves (chard) (Leaves of beetroot)	0.05*
900000	9. SUGAR PLANTS	
900010	Sugar beet (root)	0.5

* indicates that the input value is proposed at the limit of analytical quantification

sum of ethofumesate and the metabolite NC 9607 (2,3-dihydro-3,3-dimethyl-2-oxo-benzofuran-5-yl methane sulphonate) expressed as ethofumesate

Based on the proposed residue definition for risk assessment and enforcement in plant materials - the calculated total residues of ethofumesate, consisting of the sum of the residues of ethofumesate and the metabolite NC 20645, in free and conjugated form, and the metabolite NC 9607 - and on the studies presented in the dossier, the existing MRL values for the sugar beet evaluated and new MRLs were proposed for beetroots (body and leaves) from extrapolation from sugar beets.

The results from the supervised residue trials and the MRL proposals are summarised in the table below.

Table 2.7-8 Summary on data from the supervised residue trials northern and southern Europe

Crop	Region	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs	OECD calculations, unrounded mg/kg	MRL proposals (mg/kg)	existing MRL (mg/kg)	HR (mg/kg)	STMRL (mg/kg)
Beetroots		extrapolation from sugar beets		0.2	0.1		
sugar beet leaves	NEU	8x<0.02, 11x<0.06, 0.06, 0.07, 9x<0.1, <0.12, 0.18	0.22	0.3	0.05*	0.18	0.06
Chard/beet leaves	SEU	6x<0.02, 0.04, 0.06, 0.14	0.20	0.2	0.05*	0.14	0.02
sugar beet roots	NEU	8x<0.02, 14x<0.06, 0.09, 11x<0.1	0.19	0.2	0.5	0.1	0.06
	SEU	8x<0.02, 3x<0.06	0.06	0.06	0.5	0.06	0.02

* indicates that the input value is proposed at the limit of analytical quantification

2.7.11. Proposed import tolerances and compliance with existing import tolerances

No import tolerances were intended in the framework of the renewal process.

2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1. Summary of fate and behaviour in soil

In the aerobic metabolism studies evaluated in the course of the first approval, ethofumesate was slowly degraded (lab DT₅₀ between 47 and 211 days; median = 84 d; n = 10). The main degradation products were carbon dioxide and non-extractable residues. Ethofumesate was degraded in soil through the action of soil micro flora via dealkylation (NC 8493, ethofumesate- 2- hydroxy) followed by oxidation (NC 9607, ethofumesate-lactone) and ring opening (NC 20645, ethofumesate-carboxylic acid). These studies, however, were often characterized by inappropriate handling of the experimental soils (storage of the soils outdoors or under ambient conditions for up to three months, low microbial biomass levels, no pre-incubation prior application of the spiking solutions). The newly submitted aerobic soil degradation studies confirmed the previously established degradation route, but degradation was faster due to the use of freshly sampled soils. Considering the valid laboratory degradation studies from the previous evaluation and the new studies, ethofumesate was generally moderately fast degraded (DT_{50lab}: 9.4 – 137 d; geomean = 18.7 d; n=17). The main degradation products were carbon dioxide and non-extractable residues. Ethofumesate is degraded to NC 8493 (ethofumesate- 2- hydroxy) followed by NC 9607 (ethofumesate-lactone) and NC 20645 (ethofumesate-carboxylic acid) or the loss of the methanesulfonate moiety to transient degradates which are converted to non-extractable residues (21 - 64% AR; n = 17) and mineralized to CO₂ (4 - 60% AR; n = 17) at 100 days. Metabolites were detected in minor amounts only (< 5% AR).

Under anaerobic conditions, ethofumesate was not mineralized (CO₂-evolvment during anaerobiosis < 2.5 % AR after 152 days). It was regarded as stable and therefore the anaerobic degradation is not considered to contribute significantly to the degradation route of ethofumesate.

In the photolysis in soil studies submitted for the first approval, the DT₅₀ of ethofumesate in soil under environmental conditions ranged between 65 days and 13.8 days. In the first study one main phototransformation product was identified (NC 8493 with maximum amounts of about 30%). This metabolite was also observed as transient metabolite in the soil metabolism study. One minor product < 5% was formed. In the second study,

three radioactive fractions were detected but not identified (D2, D3 < 5%, D4 at 7.1% AR at day 30). The photolysis in soil studies were repeated due to experimental insufficiencies and the occurrence of considerable levels of unidentified radioactivity. In the new studies, the main transformation product was NC 8493 (max. 24.2%). A second minor transformation product was identified as NC 20645 (max. 4.8%). All other metabolites did not exceed 1%.

Ethofumesate was rapidly and strongly adsorbed to soil in laboratory tests with K_{foc} ranging between 97 and 208 mL/g (geomean 118 mL/g; $n = 12$). An additional time-dependent sorption study was submitted by the notifier Taskforce. The increase of sorption over time was defined as the ratio of concentration of [Phenyl-UL-14C]Ethofumesate in soil to the concentration in aqueous 0.01 M CaCl_2 extracts (R_{TDS} value). At study end (91 days), the mean R_{TDS} value increased by a factor of 1.4-3.0 indicating effects of ageing on adsorption of ethofumesate. Adsorption to soil of the metabolites NC 8493 and NC 20645 was investigated. Due to the fast degradation of these metabolites, K_{oc} could not be determined for NC 8493 with batch equilibrium tests and was instead estimated via EPI WIN to 20.82 mL/g. For NC 20645 (ethofumesate-carboxylic acid) the K_{foc} could be determined in 4 of 5 investigated soils. The adsorption to soil was low (geomean K_{FOC} : 5.1 mL/g).

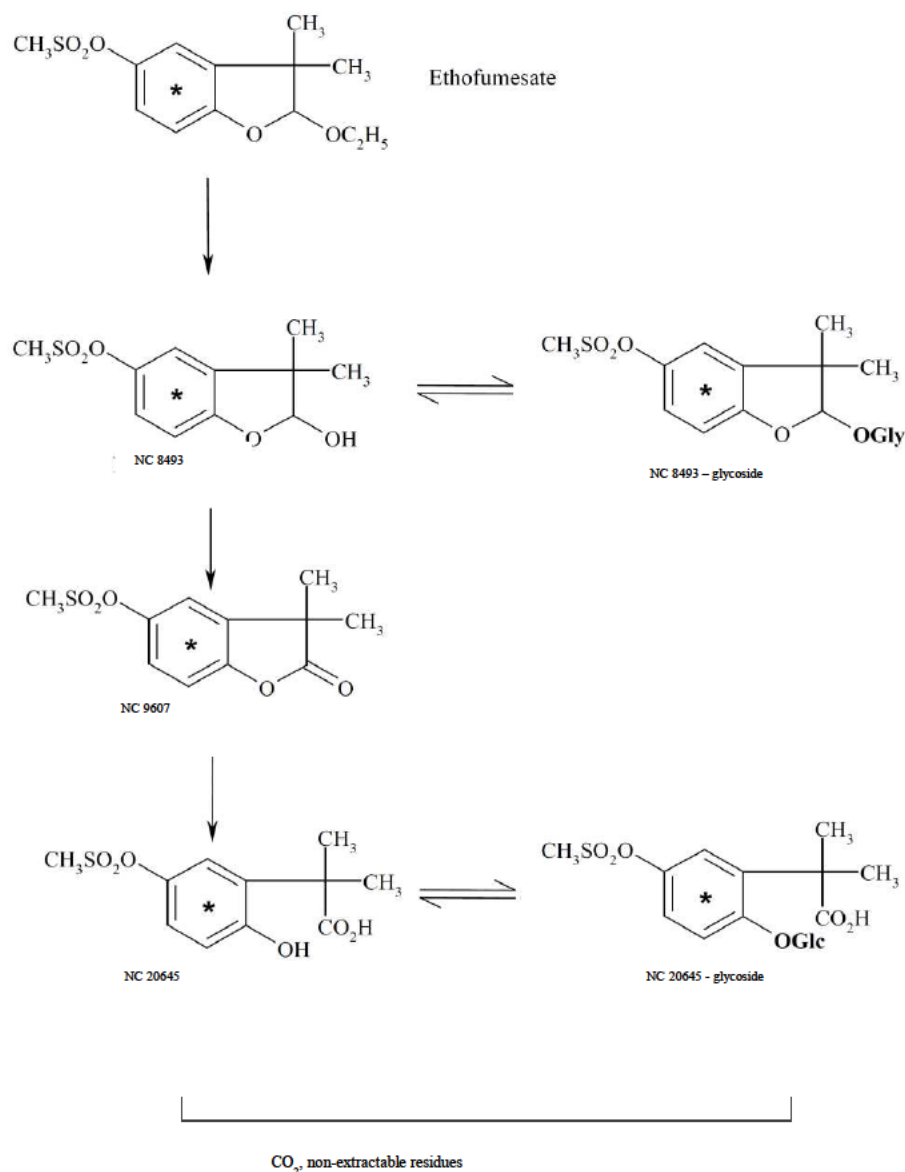
Due to several experimental deficiencies, only one column study could be regarded as valid. In this study, aged ethofumesate residue (corresponding to a field rate of 7.25 kg/ha) was leached with a CaCl_2 -solution simulating approximately 500mm of artificial rain. Over the study period, 2.7% of the AR - mainly consisting of ethofumesate and NC20645 - were found in the leachate.

In the course of the first approval of ethofumesate, 5 lysimeter studies covering a period of two or three years with either one or two applications of ethofumesate were evaluated. Spring application rates of 1.25 and 1.5 kg/ha were studied in lysimeters planted with sugar or fodder beet followed by wheat. Mean annual precipitation ranged between 857 and 820 mm/year. Ethofumesate was not detected in the leachate of any of the lysimeter and at termination of the studies the majority of the radioactivity remained in the top 30 cm of the soil layers. Concentrations below 0.1 $\mu\text{g/L}$ of NC9607 were observed in some leachates. The majority of the radioactivity in the leachate was attributed to ethofumesate derived fragments metabolized by soil micro-organisms and subsequently incorporated into soil organic matter. However, in one study an individual peak ("Peak A") was identified. The highest maximum concentration was 0.5 $\mu\text{g/L}$ (annual mean, calculated as a.s. equivalent). It was not evaluated whether this peak consisted of one or more components. In a targeted study, the notifier Taskforce could identify the structure of both metabolites potentially representing Peak A as glycoside conjugates of the respective soil metabolites NC 8493 and NC 20645. Two new lysimeter studies were submitted by the notifier UPL. In the first study, Ethofumesate and its degradation products did not exceed 0.1 $\mu\text{g/L}$ in the leachate. In this two year study, unidentified polar material – attributable neither to ethofumesate nor to NC9607 - ranged between 0.7 and 1.89 $\mu\text{g/L}$ parent equivalents. Similar results were obtained in the second lysimeter study, where the concentration in the leachate was similar and the majority of Ethofumesate was incorporated into large organic structures. Furthermore, up to 14 unknown fractions were detected in this two year study and none exceeded 0.1 $\mu\text{g/L}$ (annual average concentrations). Therefore, it can be assumed that also in the first study the unidentified polar material belongs to a larger number of fractions.

Metabolites NC 20645 and NC8493 and/or their respective glycoside conjugate were considered to represent the Peak A detected in Lysimeter studies carried out for the first approval of ethofumesate. The theoretically possible back reaction of NC 20645 to NC 9607 was investigated and was shown not to contribute significantly to the degradation of NC20645. Degradation rates of the soil metabolites NC 8493, NC 9607 and NC 20645 were determined in three separate studies. The DT_{50} were less than 1.5 hours for NC 8493, NC 9607 and 1-3 hours for NC 20645. This fast degradation is in line with the observed very low occurrence in the aerobic soil metabolism studies. The groundwater risk assessment was carried out for both NC20645 and NC8493 as the respective aglycon.

For the first approval of ethofumesate, several field studies were submitted. In the previous list of endpoints, values for 13 sites were included with DT_{50} values (not normalized) of 15 to 250 days with a mean of 77 days and a median of 56 days. Several of these studies were not considered acceptable after the current re-evaluation due to insufficient sampling depth. In addition to the existing field studies, the notifier UPL submitted new field studies. A total of 13 field dissipation studies is now available with half-lives ranging between 10.2 – 157 d and normalized DT_{50} ranging between 13.5 – 112 days (geomean = 40.7 days). Since DT_{50} from field studies were shown not to be statistically different from the laboratory degradation studies' population, the combined geomean of laboratory and field studies (26.2 days) was used in the further groundwater and surface water assessment.

Proposed transformation pathway in soil



The behaviour of both enantiomers of ethofumesate was exemplarily investigated under laboratory conditions in soil and water/sediment. The degradation was not enantioselective. In one scientific paper, the potentially enantioselective degradation of ethofumesate was investigated in four Chinese soils under laboratory conditions. No significant difference was observed in three out of four soils. In one of the four soils, a minor difference (max. enantiomeric ratio: 1.65) was observed. In this soil, the half-life of the (+) enantiomer was in the typical range of the other soils, whereas the half-life of the (-) enantiomer was faster. The reliability of this study for regulatory purposes is not given. Therefore, it is considered adequate that all studies on the active substance were performed using the racemic mixture.

2.8.2. Summary of fate and behaviour in water and sediment

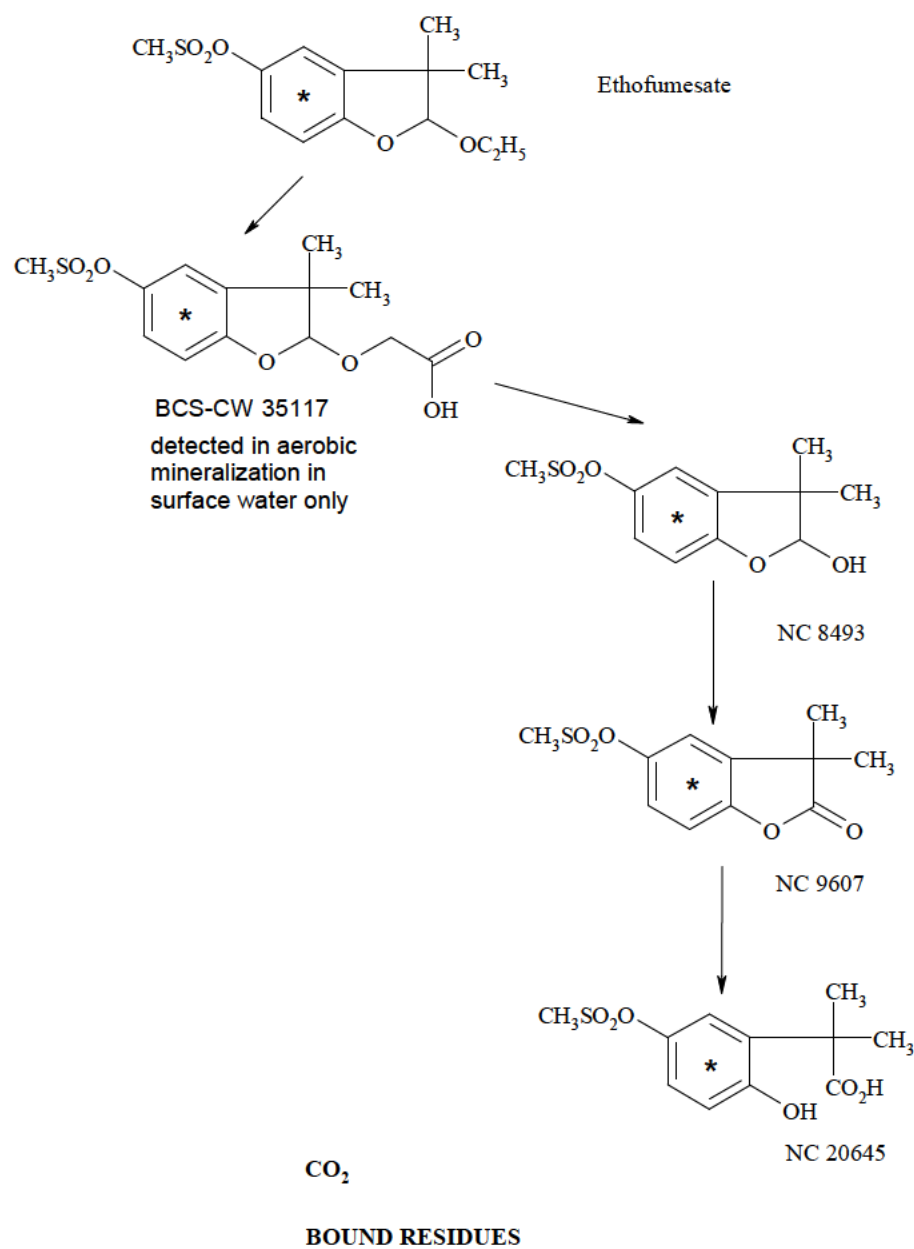
Ethofumesate is stable to hydrolysis at pH 4, pH 7 and pH 9. No major degradation products were observed.

In the first evaluation for approval, the photolytic degradation of ethofumesate was reported for a number of studies with variable results. Aqueous photolysis at pH 7 with filtered light from an Hg-arc lamp resulted in a DT₅₀ of 28-31 hours (3-5 fold intensity of natural sunlight) in irradiated solutions. However, due to 41% of unidentified radioactivity in this study and experimental deficiencies in other aqueous photolysis studies, new studies were conducted by both notifiers. In both new aqueous photolysis studies, a multitude of transformation products was formed; none of them exceeding 10% AR. A similar degradation pattern is observed in a study investigating the photolysis of ethofumesate in natural water, which was performed for registration in Japan and is an optional data requirement. The results mirrored the findings of the study on aqueous photolysis in buffered solution. A large number of unidentified photodegradates were formed, two of them above 5% AR.

Contrasting results were reported for the new aerobic mineralization studies in water. In the study by the notifier UPL, ethofumesate was found to be stable in natural surface water until day 62 of incubation and the mineralisation was marginal with a maximum of 1.1% (high-dose test) and 0.8% (low-dose test) at the end of the incubation period. The new study on aerobic mineralization in surface water submitted by the notifier Taskforce, however, showed that after a lag phase of 60 days a significant degradation of ethofumesate was observed: the remaining amounts of ethofumesate after 88 days were 58.3% AR and 79.3% AR in the low- (10 µg/L) and high-dose (100 µg/L) experiment, respectively. The main metabolite formed was NC 8493 (ethofumesate-2-hydroxy) with a maximum amount of 18.3% AR. The metabolite identified as BCS CW35117 (ethofumesate acetic acid) was formed at 13.4% AR and 2.4% AR in the low-dose and high-dose experiment, respectively.

Three dark water/sediment studies submitted for the previous evaluation were found to be not valid anymore, mainly due to experimental insufficiencies. For instance, in two of these studies only the pH of the water phase was reported whereas in one study only the sediment pH was determined. In addition, metabolites above 10% AR were not identified within these studies. Therefore, new water sediment studies were submitted by both notifiers. Mineralisation of the active substance ranged between 1.2 % AR and 15.3% AR after 103 and 125 days, respectively. Non-extractable residues in the sediment compartment ranged between 14.2 % AR and 43.2% AR at study end. Whole system half-lives ranged between 89 and 294 days (geomean 170 d; n = 8). In both new studies, NC20645 was identified as a major metabolite (max. occurrence in whole system 18.8% AR after 125 days). However, metabolite NC20645 did not reach the maximum occurrence at study end in two out of four water/sediment systems.

Figure 2-1: Degradation pathway of ethofumesate in water/sediment systems



2.8.3. Summary of fate and behaviour in air

The vapour pressure of ethofumesate is 0.00065 Pa at 25°C indicating a moderate potential for volatilization from plant and soil. Since the compound is rapidly degraded in air ($DT_{50} = 4.1$ hours), no further investigation of its transport in air is required. It is unlikely that the compound is transported in air over long distances or accumulates in air.

2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

The monitoring for the presence of ethofumesate in groundwater following the use on sugar beet has been requested by the Spanish Registration Authorities. The notifier Taskforce carried out a monitoring study in the regions "Medina del Campo" and "Arévalo", both in Castile and León. They are part of a tableland in the centre of the Iberian Peninsula called "Meseta Central", that is at the same time the basin of the river Duero. The river basin is the most important production area of sugar beet in Spain. The concentrations of ethofumesate in the eight groundwater samples from five locations were all below 0.05 µg/L. However, in order to be more convincing and conclusive, a more comprehensive and representative sampling campaign would have been needed. The actual vulnerability of the sites should have been set into context with the relevant FOCUS groundwater scenarios, hydraulic connectivity with the fields where ethofumesate was applied and the actual pesticide use (e.g. from farmer surveys) should have been determined.

Several scientific papers on surface and groundwater monitoring were retrieved and submitted by the notifier Taskforce. In a comprehensive and fully reliable study on the occurrence of 331 organic pollutants in rivers from North Germany, between 1994 and 2004 ethofumesate was never detected above the LOQ.

In a study from Spain, water samples from ninety two sampling points (13 surface and 79 ground water) were analysed. Ethofumesate was present in 60-80% of the samples at concentrations < 0.1 µg/L (mean about 0.032 – 0.038 µg/L) with one exception (0.133 µg/L). However, it is unknown whether the maximum concentration is from a groundwater or surface water sample.

Ethofumesate concentrations in air samples from rural and urban areas were investigated in a French monitoring study. Ethofumesate was detected in 2% of the ambient air samples and concentrations ranged between 0.54 and 1.16 ng/m³. In a study investigating the temporal variations of currently used pesticides in Strasbourg (France), Ethofumesate was found at concentrations ranging between 0.07 and 1.13 ng/L. However, without exact knowledge of the application times, no reliable conclusions on potential vaporization of ethofumesate can be drawn. From the study report it is unclear how representative such a site is for regulatory purposes.

2.8.5. Definition of the residues in the environment requiring further assessment

The residue definitions relevant for risk assessment for each compartment are the following:

Compartment	Residue Definition
Soil	ethofumesate, NC 8493(ethofumesate-2-hydroxy),
Groundwater	ethofumesate, NC 8493(ethofumesate-2-hydroxy) NC 20645 (ethofumesate-carboxylic acid)
Surface Water	ethofumesate, NC 8493(ethofumesate-2-hydroxy) NC 20645 (ethofumesate-carboxylic acid) BCS-CW35117 (ethofumesate-acetic acid)
Sediment	ethofumesate, NC 20645 (ethofumesate-carboxylic acid)

2.8.6. Summary of exposure calculations and product assessment

2.8.6.1. PEC Soil

Following the FOCUS kinetics group guidance, the best fit kinetics was used as persistence endpoints to trigger further studies. In this case, the non-normalized DT50 from the field study in Weeze (Germany) was considered as a worst case. PEC soil for the soil photolysis metabolite NC 8493 was calculated based on its maximum occurrence in soil (24.2% AR; molecular weight rel. to parent of 0.902) and its worst case DT50. PEC_{plateau} was not triggered.

2.8.6.2. PECGW

Calculations were carried taking into account applications every three years (as indicated in the GAP). Based on the “EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil”, a combined laboratory and field DT50 for ethofumesate was used for PEGW calculations. The soil photolysis metabolite NC8493 was calculated as pseudo-application whereas NC 20645 was assumed to be formed from NC8493 with a formation fraction of 1 (worst case assumption). Application every third year was calculated.

The leaching simulations resulted in PEC_{GW} values below 0.1 µg L⁻¹ for ethofumesate and its metabolites NC8493 and NC20645 for all intended uses and all relevant FOCUS scenarios using FOCUS PEARL. The risk for groundwater leaching is considered to be low. No relevance assessment of metabolites is needed.

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m) for pre-emergence application 1x1000g/ha every three years.

Model/Crop	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			NC20645	NC8493
	Chateaudun	0.024	<0.001	<0.001
	Hamburg	0.011	<0.001	<0.001
	Jokioinen	0.001	<0.001	<0.001
	Kremsmunster	0.008	<0.001	<0.001
	Okehampton	0.014	<0.001	<0.001
	Piacenza	0.014	<0.001	<0.001
	Porto	0.002	<0.001	<0.001
	Sevilla	<0.001	<0.001	<0.001
	Thiva	<0.001	<0.001	<0.001

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m) for post-emergence application 1x1000g/ha every three years.

Model /Crop	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			NC20645	NC8493
	Chateaudun	0.031	<0.001	<0.001
	Hamburg	0.013	<0.001	<0.001
	Jokioinen	0.001	<0.001	<0.001
	Kremsmunster	0.008	<0.001	<0.001
	Okehampton	0.015	<0.001	<0.001
	Piacenza	0.015	<0.001	<0.001
	Porto	0.002	<0.001	<0.001
	Sevilla	<0.001	<0.001	<0.001
	Thiva	<0.001	<0.001	<0.001

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m) for post-emergence application 2x500g/ha every three years.

Model /Crop	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			NC20645	NC8493
	Chateaudun	0.039	<0.001	<0.001
	Hamburg	0.016	<0.001	<0.001
	Jokioinen	0.001	<0.001	<0.001
	Kremsmunster	0.010	<0.001	<0.001
	Okehampton	0.018	<0.001	<0.001
	Piacenza	0.016	<0.001	<0.001
	Porto	0.002	<0.001	<0.001
	Sevilla	0.001	<0.001	<0.001
	Thiva	<0.001	<0.001	<0.001

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m) for post-emergence application 3x333g/ha every three years.

Model / Crop	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			NC20645	NC8493
	Chateaudun	0.041	<0.001	<0.001
	Hamburg	0.017	<0.001	<0.001
	Jokioinen	0.001	<0.001	<0.001
	Kremsmunster	0.010	<0.001	<0.001
	Okehampton	0.020	<0.001	<0.001
	Piacenza	0.017	<0.001	<0.001
	Porto	0.002	<0.001	<0.001
	Sevilla	0.001	<0.001	<0.001
	Thiva	0.001	<0.001	<0.001

2.8.6.3. PECSW/SED

For all uses, predicted environmental concentrations in surface water and sediment (PEC_{sw} and PEC_{sed}) for ethofumesate and its metabolites NC20645, NC 8493, and CW35117 were calculated using FOCUS Step 1 and 2. For the parent, further Step 3 calculations were needed. These were carried out with the FOCUS Swash software package (Swash 3.1; Macro 5.5.3; PRZM 3.5.2; TOXSWA 2.6). Risk mitigation measures were included following the FOCUS landscape and mitigation report (calculations were carried out with SWAN).

No other routes of exposure were identified.

2.9. EFFECTS ON NON-TARGET SPECIES

2.9.1. Summary of effects on birds and other terrestrial vertebrates

Ethofumesate was found to be of low acute toxicity when tested in different species of birds and mammals; single oral dosages of >2000 mg/kg bw were generally tolerated without mortality. No critical findings were obtained in repeated dose and reproductive toxicity studies performed in quails, ducks and rats.

The acute and long-term/reproductive risks for birds and wild mammals that would result from intended uses of ethofumesate were assessed in accordance to the most recent guidance from EFSA (EFSA Journal 2009;7(12):1438). For this the following ecotoxicological endpoints have been used.

	Acute endpoint (LD ₅₀)	Reproductive endpoint (NOAEL)
Birds	> 2000 mg ai/kg bw > 3776 (extrapolated)	265 mg ai/kg bw/d
Mammals	> 5000 mg ai/kg bw	60.9 mg ai/kg bw/d ^a

^a The reproductive endpoint of 1000 ppm is based on adverse effects on the parents (↓ body weight gain), the offspring (number of male pups, life birth index P_0 , 21 day survival index in P_0) and the reproduction (↓ mean litter size in P_0 , ↑ pre-implantation loss in P_0 generation). The actual daily dose of 60.9 mg ai/kg bw/d is based on a statistically significant decrease in body weight gain in male rats (> 10% compared to the control in the P_0 generation males and in the P_1 generation males, mainly at the beginning of the study).

Endocrine disrupting properties:

Wild mammals

A detailed analysis of all the apical toxicological studies (subchronic, chronic / oncogenicity, reproduction and developmental toxicity) on ethofumesate revealed no evidence of any reproducible endocrine effect. Therefore, based on a complete toxicological data set, there is no evidence of any endocrine disrupting potential of ethofumesate in mammals.

Birds

The population relevant effects of ethofumesate on birds were studied in reproductive toxicity studies on bobwhite quail and mallard ducks. For both species there were no effects on adult birds, offspring or reproductive parameters up to and including the highest test level of 3000 ppm a.s. As reproduction was not affected in two avian species, it is concluded that there are no population relevant adverse effects of ethofumesate. No additional studies are deemed necessary.

Amphibians and Reptiles

Currently no test methods are established to assess the population relevant effects of chemicals to amphibians or reptiles. Under consideration of the overall favourable toxicological profile of ethofumesate in birds and mammals, no adverse effects are to be expected for reptiles and amphibians under field conditions.

2.9.2. Summary of effects on aquatic organisms

Active substance:

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC ₅₀ /LC ₅₀ [mg/L]	Reference
Fish							
<i>Oncorhynchus mykiss</i> Rainbow trout	Semi-static	96 h	Mortality	n	9.7	26.5	██████████ 1991a ^a
<i>Oncorhynchus mykiss</i> Rainbow trout	Semi-static	96 h	Mortality	mm	4.125	11.91	██████████. et al., 1989
<i>Lepomis macrochirus</i> Bluegill sunfish	Semi-static	96 h	Mortality	n	15.0	21.2	██████████ 1991b
<i>Lepomis macrochirus</i> Bluegill sunfish	Semi-static	96 h	Mortality	mm	3.55	12.37	██████████ et al., 1990
<i>Cyprinodon variegatus</i> Sheepshead minnow	Static	96 h	Mortality	n	12.0	25.0	██████████ ██████████ 1992
<i>Cyprinus carpio</i>	Semi-static	96 h	Mortality	mm	6.51	10.92	██████████. et

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC ₅₀ /LC ₅₀ [mg/L]	Reference
Mirror carp							al., 1989
<i>Leuciscus idus</i> Golden orfe	Static	96 h	Mortality	n	9.3	22.0	█ 1993 ^a
<i>Danio rerio</i> Zebrafish	Flow-through	FFLC	Reproduction Growth	mm	1.25 0.156	-	█ 2013
<i>Pimephales promelas</i> Fathead minnow	Flow-through	ELS (28 d)	Mortality Growth	mm	13.3 4.17	-	█ 1991
Aquatic invertebrates							
<i>Daphnia magna</i> Waterflea	Static	48 h	Immobility	n	13.0	28.1	Thun, S., 1993
<i>Americamysis bahia</i> Mysid shrimp	Static	96 h	Immobility	mm	< 2.5	5.4	Schupner, J.K. & Stachura, B.J., 1992
<i>Crassostrea virginica</i> Eastern oyster	Flow-through	96 h	Mortality Shell growth	mm	5.6 < 0.81	> 9.0 1.7	Yurk, J.J. & Ache, B.W., 1992
<i>Daphnia magna</i> Waterflea	Semi-static	21 d	Reproduction	n	0.32	0.77	Douglas, M.T., James, C.M. & Macdonald, I.A., 1990
<i>Daphnia magna</i> Waterflea	Semi-static	21 d	Reproduction	n	1.0	2.7	Bellmann, W., 1992 ^a
<i>Daphnia magna</i> Waterflea	Semi-static	21 d	Reproduction	mm	0.25	1.2	Adema, D.M.M. & de Rulter, A., 1989 ^a
Sediment dwelling organisms							
<i>Chironomus riparius</i> Midge	Static	28 d	Emergence	mm	3.2	> 3.2	Mattock, S.D., 1998
<i>Chironomus riparius</i> Midge	Static	28 d	Emergence Development	mm	2.42	> 2.42	Desmares- Koopmans, M.J.E., 2002
<i>Chironomus riparius</i> Midge	Static	28 d	Emergence Development	mm	12.9	> 33.0	Stäbler, D., 2003
Algae							
<i>Pseudokirchneriella subcapitata</i> Green algae	Static	72 h	Growth rate Yield	mm	5.91	16.3 9.68	Bruns, E., 2008
<i>Anabaena flos-aquae</i> Blue green algae	Static	96 h	Growth rate Biomass	n	20.0	> 20.0	Banman, C.S., Daly, R.A. & Lam, C.V., 2009a
<i>Skeletonema costatum</i> Saltwater diatom	Static	72 h	Growth rate Biomass	n	5.0 2.5	> 20.0 14.5	Banman, C.S., Daly, R.A. & Lam, C.V., 2009b
		96 h	Growth rate Biomass	n	10.0 5.0	> 20.0 17.1	
Aquatic macrophytes							

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC ₅₀ /LC ₅₀ [mg/L]	Reference
<i>Lemna minor</i> Duckweed	Semi-static	14 d	Growth rate Biomass	mm	4.3	> 52.8 50.4	Scheerbaum, D., 1998
<i>Lemna minor</i> Duckweed	Semi-static	7 d	Growth rate Biomass	mm	26.0 17.0	> 42.0 35.0	Bogers, M., 2001
<i>Myriophyllum spicatum</i> Water milfoil	Static	14 d	Growth rate Yield	mm	0.036	0.479 0.25	Banman, C.S., 2013

n...nominal, mm...mean measured

^a Due to deficiencies observed in the study the results of study should be used as additional information only.

Metabolites:

Effects to aquatic organisms from exposure to the metabolites NC 8493 and NC 20643 were tested for the aquatic invertebrates and algae. No studies were conducted with fish and aquatic macrophytes.

Under consideration of the high sensitivity of the parent compound ethofumesate to algae and aquatic macrophytes no studies on fish are considered necessary. However, to address the risk to aquatic macrophytes a 10 times higher toxicity of the metabolites compared to the parent compound is considered in the risk assessment.

An additional metabolite was found in a water sediment study submitted by the Task Force Ethofumesate. The metabolite was measured at concentrations > 10% and hence an aquatic risk assessment has to be conducted.

The notifier Task Force Ethofumesate submitted studies with aquatic invertebrates and algae. For the aquatic macrophytes a ten times higher toxicity compared to the parent compound was assumed.

United Phosphorous Ltd. submitted no additional studies as the metabolite Ethofumesate acetic acid was not identified in the water sediment study conducted by UPL.

Test substance	Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC ₅₀ /LC ₅₀ [mg/L]	Reference
Aquatic invertebrates								
Metabolite NC 8493	<i>Daphnia magna</i> Waterflea	Semi-static ^a	48 h	Immobility	n	10	> 10	Riebschläger, T., 2012a
Metabolite NC 8493	<i>Daphnia magna</i> Waterflea	Static ^a	48 h	Immobility	n	100	> 100	Juckeland, D., 2013a
Metabolite NC 20645	<i>Daphnia magna</i> Waterflea	Semi-static ^a	48 h	Immobility	n	10	> 10	Riebschläger, T., 2012b
Metabolite NC 20645	<i>Daphnia magna</i> Waterflea	Static ^a	48 h	Immobility	n	100	> 100	Juckeland, D., 2013b
Metabolite Ethofumesate acetic acid	<i>Daphnia magna</i> Waterflea	Static ^a	48 h	Immobility	n	10	> 10	König, N., 2013
Algae								
Metabolite NC 8493	<i>P. subcapitata</i> Green algae	Static	72 h	Growth rate Yield	n	0.367	20.7 0.865	Bruns, E., 2012a

Test substance	Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC ₅₀ /LC ₅₀ [mg/L]	Reference
Metabolite NC 8493	<i>D. subspicatus</i> Green algae	Static	72 h	Growth rate Yield	mm	1.33	4.83 1.87	Juckeland, D., 2013c
Metabolite NC 20645	<i>P. subcapitata</i> Green algae	Static ^a	72 h	Growth rate Yield	n	10.0	> 10.0	Bruns, E., 2012b
Metabolite NC 20645	<i>D. subspicatus</i> Green algae	Static	72 h	Growth rate Yield	mm	1.25	52.4 8.83	Juckeland, D., 2013d
Metabolite Ethofumesate acetic acid	<i>P. subcapitata</i> Green algae	Static	72 h	Growth rate Yield	n	25	> 100 98.98	Sobczyk, H., 2013

n...nominal, mm...mean measured

^a Limit testRepresentative formulations:**Ethofumesate 500 SC**

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg ai/L]	EC ₅₀ /LC ₅₀ [mg ai/L]	Reference
Fish							
<i>Cyprinus carpio</i> Mirror carp	Semi-static	96 h	Mortality	mm	5.7	14.4	██████ et al., 1989
<i>Danio rerio</i> Zebra fish	Semi-static	96 h	Mortality	n	9.0	34.0	██████ et al., 1988
Aquatic invertebrates							
<i>Daphnia magna</i> Waterflea	Static	48 h	Immobility	n	19.57	26.8	Cameron, B.D., et al., 1989
<i>Daphnia magna</i> Waterflea	Semi-static	21 d	Reproduction	n	0.32	1.2	Barber, I., 1991
Algae							
<i>Desmodesmus subspicatus</i> Green algae	Static	72 h	Growth rate Biomass	n	2.2	9.7 6.7	Knacker, T., 1989
Aquatic macrophytes							
<i>Myriophyllum spicatum</i> Water milfoil	Static	14 d	Growth rate Yield	n	0.005	0.38 0.05	Banman, C.S., 2012

Ethofol 500 SC

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg ai/L]	EC ₅₀ /LC ₅₀ [mg ai/L]	Reference
Fish							
<i>Oncorhynchus mykiss</i> Rainbow trout	Static	96 h	Mortality	mm	2.2	> 13.9 < 22.1	██████ ████████ 1997
Aquatic invertebrates							
<i>Daphnia magna</i> Waterflea	Static	48 h	Immobility	n	12.0	24.0	Pors, J., 1997a
Algae							
<i>Raphidocelis</i>	Static	72 h	Growth rate	n	0.92	13.6	Ruymen, V.,

Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg ai/L]	EC ₅₀ /LC ₅₀ [mg ai/L]	Reference
<i>capricornutum</i> Green algae			Biomass		< 0.92	5.2	2003
Aquatic macrophytes							
<i>Lemna minor</i> Duckweed	Static	7 d	Growth rate Yield (frond number)	n	10.0 10.0	80.6 44.0	Hoffmann, K. & Deierling, T., 2010
			Growth rate Yield (dry weight)		10 3.2	> 100 43.1	
<i>Myriophyllum aquaticum</i> Water milfoil	Static	7 d	Growth rate Yield (fresh weight)	mm	0.908 0.908	16.1 2.87	Scheerbaum, D., 2013

n...nominal, mm...mean measured

2.9.3. Summary of effects on arthropods

Effects on bees

Acute oral and contact toxicity to honey-bees from exposure to the active substance and the representative formulations Ethofumesate 500 SC (Task Force Ethofumesate) and Ethofol 500 SC (United Phosphorous Ltd.).

Test substance	Exposure route	Endpoint	Toxicity	Reference
Ethofumesate tech.	Acute oral Acute contact	48 h LD ₅₀	> 50 µg ai/bee > 50 µg ai/bee	Barrett, K.L., 1991
	Acute oral Acute contact	48 h LD ₅₀	> 100 µg ai/bee > 100 µg ai/bee	Cole, J.H., 1992
	Acute oral Acute contact	48 h LD ₅₀	> 106.3 µg ai/bee > 100 µg ai/bee	Schmitzer, S., 2011a
Ethofumesate 500 SC	Acute oral Acute contact	48 h LD ₅₀	> 108.8 µg ai/bee > 100 µg ai/bee	Schmitzer, S., 2011b
Ethofol 500 SC	Acute oral	48 h LD ₅₀	> 184.3 µg ai/bee	Mallikarjunappa, S., 1998
Ethofol 500 SC	Acute contact	48 h LD ₅₀	> 87.4 µg ai/bee	Schmitzer, S., 2010

In addition studies on the chronic oral toxicity to adult honey-bees (10 day exposure) and honey-bee brood were conducted.

Test substance	Exposure route	Endpoint	Toxicity	Reference
Ethofumesate tech.	Chronic oral	10 d LC ₅₀ 10 d NOEC	> 120 mg ai/kg 120 mg ai/kg (= 4.4 µg ai/bee/d)	Kling, A., 2013
Ethofol 500 SC	Chronic oral	10 d LC ₅₀ 10 d NOEC	> 311.6 µg ai/bee/d 311.6 µg ai/bee/d	Kleebaum, K. 2014

Effects on honey-bees and honey-bee brood

Test substance	Exposure route	Results	Reference
Ethofumesate 500 SC	Honeybee brood feeding	No adverse effects on mortality, bee brood development (eggs, young larvae, old larvae, pupae) and colony development by feeding honey bee colonies sugar syrup at a concentration typically present in the spray tank (2500 ppm)	Schmitzer, S., 2013
Ethofol 500 SC	Honeybee brood feeding	No adverse effects on mortality, bee brood development (eggs, young larvae, old larvae, pupae) and colony development by feeding honey bee colonies sugar syrup at a concentration of 1.16 kg prod./ha, equivalent to 500 g ai/ha.	Schmitzer, S., 2012

Effects on non-target arthropods other than bees

Laboratory studies with the standard arthropod species *Aphidius rhopalosiphi* and *Typhlodromus pyri* were submitted with both representative formulations.

Test species	Exposure	Test item	Rate [g ai/ha]	Type of effect	Effect [%]	Reference
<i>Aphidius rhopalosiphi</i> (adults)	contact with dried residues on treated glass plates	Ethofumesate 500 SC	500 1000	Corrected mortality / Reproduction	- 8.3 / - 68.3 - 8.0 / 18.7	Waltersdorfer, A., 2002a
				48 h LR ₅₀ > 1000 g ai/ha 48 h ER ₅₀ > 1000 g ai/ha		
<i>Typhlodromus pyri</i> (protonymphs)	contact with dried residues on treated glass plates	Ethofumesate 500 SC	1000	Corrected mortality / Reproduction	2.1 / 16.4 *	Waltersdorfer, A., 2002b
				7 days LR ₅₀ > 1000 g ai/ha 14 d ER ₅₀ < 1000 g ai/ha		
<i>Aphidius rhopalosiphi</i> (adults)	contact with dried residues on treated glass plates	Ethofol 500 SC	125 250 500 1000 2000	Corrected mortality / Reproduction	0.0 / 10.9 0.0 / 7.4 0.0 / 5.2 0.0 / 12.2 0.0 / 34.3	Moll, M., 2011
			48 h LR ₅₀ > 2000 mL prod./ha 48 h ER ₅₀ > 2000 mL prod./ha			

Test species	Exposure	Test item	Rate [g ai/ha]	Type of effect	Effect [%]	Reference
<i>Typhlodromus pyri</i> (protonymphs)	contact with dried residues on treated glass plates	Ethofol 500 SC	125	Corrected mortality / Reproduction	6.8 / 18.9	Schwarz, A., 2011
			250		47.5 / 30.2	
			500		11.9 / 25.5	
			1000		16.9 / 31.1	
			2000		10.2 / 17.0	
					7 days LR ₅₀ > 2000 mL prod./ha	
					14 d ER ₅₀ > 2000 mL prod./ha	

In addition, laboratory studies with three additional arthropod species relevant for the proposed GAP uses were submitted.

Test species	Exposure	Test item	Rate [g ai/ha]	Type of effect	Effect [%]	Reference
<i>Aleochara bilineata</i> (adults)	contact with dried residues on sand	Tramat 500 SC	1252.5 (2.5 L prod./ha)	Mortality / Reproduction	8.0% ↑ no. of eggs ↑ no. of hatched eggs	Mead- Briggs, M., 1991
					48 h ER ₅₀ > 1252.5 g ai/ha	
<i>Poecilus cupreus</i> (adults)	contact with dried residues on sand	Tramat 500 SC	2000 (4 L prod./ha)	Corrected mortality	3.3%	Römbke, J., 1990
					14 d LR ₅₀ > 2000 g ai/ha	
<i>Chrysoperla carnea</i> (larvae)	contact with dried residues on treated glass plates	Tramat 500 SC	2000 (4 L prod./ha)	Corrected mortality / Reproduction	0.2% ↑ no. of eggs ↑ egg-laying performance	Kühner, C., 1990
					LR ₅₀ > 2000 g ai/ha	

2.9.4. Summary of effects on non-target soil meso- and macrofauna

Species	Substance	Endpoint	Reference
<i>Eisenia fetida</i>	Metabolite NC8493	56 d NOEC = 100 mg/kg soil dw	Friedrich, S., 2012a
		56 d NOEC = 16 mg/kg soil dw	Lühns, U., 2011
	Metabolite NC 20645	56 d NOEC = 100 mg/kg soil dw	Friedrich, S., 2012b
	Ethofumesate 500 SC	56 d NOEC = 25 mg ai/kg soil dw	Sowing, P. & Gosch, H.
		56 d NOEC = 27.6 mg ai/kg soil dw	Lühns, U., 2011
	Ethofol 500 SC	56 d NOEC = 32.2 mg ai/kg soil dw	Witte, B., 2013
		56 d NOEC = 26.7 mg ai/kg soil dw	Lühns, U., 2011a
		56 d NOAEC = 10.5 mg ai/kg soil dw	Stäbler, D., 2002
<i>Folsomia candida</i>	Metabolite NC8493	28 d NOEC = 100 mg/kg soil dw	Friedrich, S., 2012c
		28 d NOEC = 556 mg/kg soil dw	Friedrich, S., 2013a
	Metabolite NC 20645	28 d NOEC = 100 mg/kg soil dw	Friedrich, S., 2013b
	Ethofumesate 500 SC	28 d NOEC = 44.1 mg ai/kg soil dw	Frommholz, U., 2011

Species	Substance	Endpoint	Reference
	Ethofol 500 SC	28 d NOEC = 26.7 mg ai/kg soil dw	Lührs, U., 2011b
<i>Hypoaspis aculeifer</i>	Metabolite NC8493	14 d NOEC = 309 mg/kg soil dw	Schulz, L., 2013
	Ethofumesate 500 SC	14 d NOEC = 441 mg ai/kg soil dw	Kratz, M.-A., 2011
	Ethofol 500 SC	14 d NOEC = 44.2 mg ai/kg soil dw	Ganßmann, M., 2012
<p>Litter bag test: Test item was the herbicide Ethofumesate SC45 (code: AE B049913 00 SC45 A203, analysed content of ai 43.8 % w/w)</p> <p>Six plots in a field (Germany) were treated with Ethofumesate SC45. Six plots served as untreated control plots. An amount of 75 g ai/ha (= 171 g prod./ha), corresponding to a plateau concentration of Ethofumesate of 0.05 mg ai/kg soil, was applied in a volume of 300 L water/ha to the treatment plots. By careful harrowing the test item was incorporated into the upper 10 cm soil layer. About 2 weeks later untreated perennial ryegrass (<i>Lolium perenne</i>) was sown onto all plots. The seed rate was 45 kg/ha. Directly after sowing 48 litter bags (12 cm x 22 cm, mesh size 8 mm) filled with 4 g of dry straw each were buried per plot. The same day an amount of 1000 g ai/ha (= 2283 g prod./ha), the calculated annual application rate of ethofumesate, was applied in a volume of 300 L water/ha to the treatment plots.</p> <p>The application of the estimated plateau concentration of ethofumesate resulted in soil residues of 42.9 µg ai/kg dry soil, which is 85.8 % of the nominal amount of 50 µg/kg. The application of the annual rate of Ethofumesate SC45 resulted in soil residues of 769 µg ai/kg dry soil, corresponding to 107 % of the nominal amount directly after the spray application.</p> <p>At no sampling time (28, 56, 108, 183 and 274 days after introduction of litterbags into the soil), a statistically significant difference in proportion of straw degradation could be observed between untreated control plots and the plots treated with Ethofumesate SC45.</p> <p>Degradation of ≥ 60 % straw in untreated control was reached 9 months (274 days) after introduction of litter bags into soil and the study was terminated. The recommended coefficient of variation of 40 % for soil litter degradation in the control plots for those data generated within the first 6 months of the study was fulfilled.</p> <p style="text-align: right;">(Lechelt-Kunze, C., 2003)</p>			

New studies on the sub-lethal effect of the representative formulations Ethofumesate SC 500 and Ethofol 500 SC on earthworms and other soil macro-organisms have been conducted to investigate the effect of the product on reproduction, mortality and growth of adult *Eisenia foetida*, *Folsomia candida* and *Hypoaspis aculeifer*.

Additional studies were conducted to assess the effects of NC8493 and NC 20645 on reproduction, mortality and growth of the earthworms and other soil macro-organisms.

2.9.5. Summary of effects on soil nitrogen transformation

Test substance	Test concentration	Time	Effects (deviation from control)	Reference
Ethofumesate techn.	0.3 mg ai/kg soil dw	42 d	< 20 %	Vonk, J.W., 1988
	3.0 mg ai/kg soil dw		< 20 %	
Ethofumesate 500 SC	3.01 mg prod./kg soil dw	42 d	- 16.0 %	Schulz, L., 2011
	30.1 mg prod./kg soil dw		- 14.3 %	
Ethofol 500 SC	2.96 mg/kg soil dw = 1.29 mg ai/kg soil dw	28 d	-4.38 %	Feil, N., 2010
	14.81 mg/kg soil dw		-18.87 %	

Test substance	Test concentration	Time	Effects (deviation from control)	Reference
	= 6.47 mg ai/kg soil			
Metabolite NC 8493	1.20 mg/kg soil dw	28 d	- 1.4 %	Schulz, L., 2013a
	12.0 mg/kg soil dw		+ 15.2 %	
Metabolite NC 20645	1.38 mg/kg soil dw	28 d	+ 6.9 %	Schulz, L., 2013b
	13.8 mg/kg soil dw		+ 6.7 %	

Nitrogen mineralisation studies were conducted with the representative formulations Ethofol 500 SC and Ethofumesate 500 SC. In addition studies with the soil metabolite NC 8493 and NC 20645 were conducted.

2.9.6. Summary of effects on terrestrial non-target higher plants

Test substance	Test organisms	Study type	Test duration	Lowest ER ₅₀ [L prod./ha]	Most sensitive species	Reference
Ethofol 500 SC	Terrestrial non-target plants (8 species)	Vegetative vigour (Tier 2)	21 d	ER ₅₀ ~ 2.0	Field bean (foliar fresh weight)	Bramby-Gunary, J., 2004a
	Terrestrial non-target plants (8 species)	Seedling emergence (Tier 2)	21 d	ER ₅₀ = 0.328	Oat (foliar fresh weight)	Bramby-Gunary, J., 2004b
Ethofumesate 500 SC	Terrestrial non-target plants (10 species)	Vegetative vigour (Tier 2)	21 d	ER ₅₀ = 1.16	Tomato (shoot dry weight)	Christ, M.T. & Abedi, J., 2003a
	Terrestrial non-target plants (10 species)	Seedling emergence (Tier 2)	21 d	ER ₅₀ = 0.70	Lettuce (shoot dry weight)	Christ, M.T. & Abedi, J., 2003b
	Terrestrial non-target plants (10 species)	Seedling emergence (Tier 2)	21 d	ER ₅₀ = 0.101	Wheat (shoot dry weight)	Gosch, H. 2009

Seedling emergence and vegetative vigour tests were conducted with the two representative formulations. Based on the results of the studies the most sensitive plant species were determined to be oat (ER₅₀ = 0.328 L prod./ha, seedling emergence) and wheat (ER₅₀ = 0.101 L prod./ha. Seedling emergence).

2.9.7. Summary of effects on other terrestrial organisms (flora and fauna)

From searching peer-reviewed literature published over the last 10 years prior to submission three adequate and reliable publications on monitoring data concerning potential adverse effects of the active substance to non-target aquatic organisms were obtained.

The publications by Berenzen et al. (2005; M-458568-01-1, KCA 8.9 / 01, also filed in KCA 7.5), Bereswill et al. (2013; M-462597-02-1, KCA 8.9 / 02, also filed in KCA 7.5.) and Liess & Von der Ohe (2005; M-458575-01-1, KCA 8.9 / 03, also filed in KCA 7.5) are exposure monitoring studies including monitoring of aquatic macroinvertebrate communities. Amongst various selected pesticides, ethofumesate residues were analytically determined in streams and toxicity of measured concentrations was assessed using the toxic unit approach (TU). For this calculation, acute *Daphnia magna* endpoints from secondary sources were used; the endpoints correspond to the EU-agreed endpoint according to EFSA review report SANCO/6503/VI/99-final (2002). Reported TU values for ethofumesate were in all cases lower than 0.01, indicating an acceptable risk when applying a standard assessment factor of 100 according to the principles of a first-tier acute risk assessment under Regulation (EU) No 1107/2009. For the ecotoxicological risk assessment concerning ethofumesate use as a plant protection product, the existing guidance under Regulation (EU) No 1107/2009 is applied. Thus, the articles are not considered to impact the risk assessment as presented.

2.9.8. Summary of effects on biological methods for sewage treatment

In the study presented during the frame of the first annex I inclusion, no adverse effects were seen at the highest concentration tested (100 mg ai/L). A new study with activated sludge has been conducted with the active substance in order to meet current regulatory requirements. Based on the newly submitted study a 3 h EC₅₀ of 1000 mg ai/L was determined.

2.9.9. Summary of product exposure and risk assessment

2.9.9.1. Risk assessment for birds

Ethofumesate 500 SC

Crop	Generic focal species	SV ₉₀	TER _A	Assessment level
Sugar beet, root & stem vegetables	Small omnivorous bird “lark”	24.0	157	Tier 1
	Small insectivorous bird “wagtail”	26.8	141	Tier 1
	Small granivorous bird “finch”	24.7	153	Tier 1

Crop	Generic focal species	SV _m	TER _{LT}	Assessment level
Sugar beet, root & stem vegetables	Small omnivorous bird “lark”	10.9	45.7	Tier 1
	Small insectivorous bird “wagtail”	11.3	44.2	Tier 1
	Small granivorous bird “finch”	11.4	44.2	Tier 1

Ethofol 500 SC

Crop	Indicator species	SV ₉₀	TER _A	Assessment level
Bare soils (BBCH < 10)	Small granivorous bird	24.7	153	Screening step
Root and stem vegetables, sugar beet	Small omnivorous bird	158.8	40	Screening step

Crop	Generic focal species	SV _m	TER _{LT}	Assessment level
Bare soils (BBCH < 10)	Small granivorous bird	11.4	44.2	Screening step
Root and stem vegetables, sugar beet	Small omnivorous bird	64.8	10.6	Screening step

2.9.9.2. Risk assessment for mammals**Ethofumesate 500 SC**

Crop	Generic focal species	SV ₉₀	TER _A	Assessment level
Sugar beet, root & stem vegetables	Small insectivorous mammal “shrew”	7.6	> 658	Tier 1
	Large herbivorous mammal “lagomorph”	35.1	> 142	Tier 1
	Small omnivorous mammal “mouse”	17.2	> 29	Tier 1

Crop	Generic focal species	SV _m	TER _{LT}	Assessment level
Sugar beet, root & stem vegetables	Small insectivorous mammal “shrew”	4.2	27.3	Tier 1
	Large herbivorous mammal “lagomorph”	14.3	8.0	Tier 1
	Small omnivorous mammal “mouse”	7.8	14.7	Tier 1

Ethofol 500 SC

Crop	Indicator species	SV ₉₀	TER _A	Assessment level
Bare soils (BBCH < 10)	Small granivorous mammal	14.4	> 347	Screening step
Root and stem vegetables, sugar beet	Small herbivorous mammal	118.4	> 71.1	Screening step

Crop	Generic focal species	SV _m	TER _{LT}	Assessment level
Bare soils (BBCH < 10)	Small granivorous mammal	6.6	17.4	Screening step
Root and stem vegetables, sugar beet	Small herbivorous mammal	48.3	3.3	Screening step

Crop	Generic focal species	SV _m	TER _{LT}	Assessment level
Sugar beet (BBCH ≤ 18)	Small insectivorous mammal “shrew”	4.2	38.1	Tier 1
	Large herbivorous mammal “lagomorph”	14.3	11.1	Tier 1
	Small omnivorous mammal “mouse”	7.8	20.3	Tier 1

2.9.9.3. Risk assessment for aquatic organisms

A summary of all TER values based on the most relevant endpoints are given in the following tables.

Ethofumesate 500 SC

Post-emergence, 1 x 1000 g ai/ha

Compound	Organisms	Time scale	FOCUS Step	TER	Trigger
Ethofumesate	Fish ^a	Acute	Step 3, R3 stream	120	100
	Fish	Long-term	Step 4, R3 stream, 20 m	11	10
	Aquatic invertebrates	Acute	Step 4, R3 stream, 20 m	116	100
	Aquatic invertebrates	Long-term	Step 4, R3 stream, 10 m	12	10
	Sediment dwelling organisms	Long-term	Step 2	27	10
	Algae ^a	Long-term	Step 1	23	10
	Aquatic macrophytes ^a	Long-term	Step 4, R3 stream, 20 m	3.4	10
		Long-term	Step 4, R3 stream, 20 m 2 x 500 g ai/ha	7.2	10
		Long-term	Step 4, R3 stream, 20 m 3 x 333 g ai/ha	11	10
NC 8493	Aquatic invertebrates	Acute	Step 1	> 141	100
	Algae	Long-term	Step 1	12.2	10
	Aquatic macrophytes	Long-term	Step 2	> 25	10
NC 20645	Aquatic invertebrates	Acute	Step 1	> 1346	100
	Algae	Long-term	Step 1	1188	10
	Aquatic macrophytes	Long-term	Step 2	15	10
Ethofumesate acetic acid	Aquatic invertebrates	Acute	Step 1	> 7353	100
	Algae	Long-term	Step 1	72779	10
	Aquatic macrophytes	Long-term	Step 1	18	10

^a The most sensitive endpoint is based on a study with the active substance (LC₅₀ = 10.92 mg ai/L)

The most sensitive aquatic species was observed to be the aquatic macrophyte *Myriophyllum spicatum*. An acceptable risk to aquatic macrophytes could only be identified if risk mitigation measures (e.g. vegetated buffer zones) are considered.

Post-emergence, single application rate (1 x 1000 g ai/ha): 5 out of 6 relevant FOCUS scenarios are safe at Step 3. No safe use could be identified for aquatic organisms for the R3 stream scenario, even under consideration of risk mitigation measures (20 m vegetated buffer strips).

Post-emergence, multiple applications (2 x 500 g ai/ha): 5 out of 6 relevant FOCUS scenarios are safe at Step 3. No safe use could be identified for aquatic organisms for the R3 stream scenario, even under consideration of risk mitigation measures (e.g. vegetated buffer strips).

Post-emergence, multiple applications (3 x 333 g ai/ha): 5 out of 6 relevant FOCUS scenarios are safe at Step 3. A safe use could be identified for aquatic organisms for the R3 stream scenario, under consideration of risk mitigation measures (e.g. 20 m vegetated buffer strips).

Ethofol 500 SC

Pre-emergence, 1 x 1000 g ai/ha

Compound	Organisms	Time scale	FOCUS Step	TER	Trigger
Ethofumesate	Fish ^a	Acute	Step 3, R1 stream	153	100
	Fish	Long-term	Step 4, R1 stream, 20 m	14	10
	Aquatic invertebrates	Acute	Step 4, R1 stream, 20 m	149	100
	Aquatic invertebrates	Long-term	Step 4, R1 stream, 10 m	15	10
	Sediment dwelling organisms	Long-term	Step 2	22	10
	Algae ^a	Long-term	Step 1	18	10
	Aquatic macrophytes	Long-term	Step 4, R1 stream, 10 m	12	10
NC 8493	Aquatic invertebrates	Acute	Step 1	> 141	100
	Algae	Long-term	Step 1	12.2	10
	Aquatic macrophytes	Long-term	Step 2	> 25	10
NC 20645	Aquatic invertebrates	Acute	Step 1	> 1346	100
	Algae	Long-term	Step 1	1188	10
	Aquatic macrophytes	Long-term	Step 2	15	10
Ethofumesate acetic acid	Aquatic invertebrates	Acute	Step 1	> 7353	100
	Algae	Long-term	Step 1	72779	10
	Aquatic macrophytes	Long-term	Step 1	18	10

^a The most sensitive endpoint is based on a study with the representative formulation.

Post-emergence, 3 x 333 g ai/ha

Compound	Organisms	Time scale	FOCUS Step	TER	Trigger
Ethofumesate	Fish ^a	Acute	Step 3, R3 stream	378	100
	Fish	Long-term	Step 4, R3 stream, 10 m	18	10
	Aquatic invertebrates	Acute	Step 4, R3 stream, 10 m	195	100
	Aquatic invertebrates	Long-term	Step 3, R3 stream	17	10
	Sediment dwelling organisms	Long-term	Step 2	31	10
	Algae ^a	Long-term	Step 1	18	10
	Aquatic macrophytes	Long-term	Step 3, R3 stream	13	10
NC 8493	Aquatic invertebrates	Acute	Step 1	> 141	100
	Algae	Long-term	Step 1	12.2	10
	Aquatic macrophytes	Long-term	Step 2	> 25	10
NC 20645	Aquatic invertebrates	Acute	Step 1	> 1346	100
	Algae	Long-term	Step 1	1188	10
	Aquatic macrophytes	Long-term	Step 2	21	10
Ethofumesate acetic acid	Aquatic invertebrates	Acute	Step 1	> 7353	100
	Algae	Long-term	Step 1	72779	10
	Aquatic macrophytes	Long-term	Step 1	18	10

^a The most sensitive endpoint is based on a study with the representative formulation.

The most sensitive aquatic species were observed to be the fish (long-term), the aquatic invertebrates (oyster) and the aquatic macrophyte *Myriophyllum spicatum*. An acceptable risk to aquatic organisms could only be identified if risk mitigation measures (i.e. 20 m vegetated buffer zones) are considered.

Pre-emergence application, 1 x 1000 g ai/ha: 5 out of 6 relevant FOCUS scenarios are safe at Step 3. A safe use could be identified for aquatic organisms for the R1 stream scenario, taking into account risk mitigation measures (i.e. 20 m vegetated buffer strips).

Post-emergence application, 3 x 333 g ai/ha: 5 out of 6 relevant FOCUS scenarios are safe at Step 3. A safe use could be identified for aquatic organisms for the R3 stream scenario, taking into account risk mitigation measures (i.e. 10 m vegetated buffer strips).

2.9.9.4. Risk assessment for bees

Ethofumesate 500 SC, 1 x 1000 g ai/ha

Acute risk to adult honey-bees:

Test substance	Exposure route	Endpoint [µg ai/bee]	Q _H	Risk acceptable?
Ethofumesate tech.	Oral	48 h LD ₅₀ > 106.3	< 9.4	Yes
	Contact	48 h LD ₅₀ > 100	< 10	Yes
Ethofumesate SC 500	Oral	48 h LD ₅₀ > 108.8	< 9.2	Yes
	Contact	48 h LD ₅₀ > 100	< 10	Yes

Chronic risk to adults honey-bees:

Endpoint	SV	ETR	Trigger	Risk acceptable?
10d LDD ₅₀ = 4.4 µg ai/bee/d	7.6 (down-ward application)	1.7	ETR > 0.03	No

Exposure	Endpoint	SV	Ef	twa	ETR	Trigger	Risk acceptable?
Field margin	10d LDD ₅₀ = 4.4 µg ai/bee/d	5.9	0.0092	0.72	0.009	ETR > 0.03	Yes
Adjacent crop		9.9	0.0033	0.72	0.005		Yes

Risk to honey-bee brood:

Test substance	Exposure route	Results	Risk acceptable?
Ethofumesate 500 SC	Honeybee brood feeding	No adverse effects on mortality, bee brood development (eggs, young larvae, old larvae, pupae) and colony development by feeding honey bee colonies sugar syrup at a concentration typically present in the spray tank (2500 ppm)	Yes

Ethofol 500 SC, 1 x 1000 g ai/ha

Acute risk to adult honey-bees:

Test substance	Exposure route	Endpoint [µg ai/bee]	Q _H	Risk acceptable?
Ethofumesate tech.	Oral	48 h LD ₅₀ > 106.3	< 9.4	Yes
	Contact	48 h LD ₅₀ > 100	< 10	Yes
Ethofumesate 500 SC	Oral	48 h LD ₅₀ > 184.3	< 5.4	Yes
Ethofol 500 SC	Contact	48 h LD ₅₀ > 87.4	< 11.4	Yes

Chronic risk to adult honey-bees

Endpoint	SV	ETR	Trigger	Risk acceptable?
10d LDD ₅₀ > 4.4 µg ai/bee/d	7.6 (down-ward application)	1.7	ETR > 0.03	No
10d LDD ₅₀ > 311.6 µg ai/bee/d	7.6 (down-ward application)	0.024	ETR > 0.03	Yes

Exposure	Endpoint	SV	Ef	twa	ETR	Trigger	Risk acceptable?
Field margin	10d LDD ₅₀ = 4.4 µg ai/bee/d	5.9	0.0092	0.72	0.009	ETR > 0.03	Yes
Adjacent crop		9.9	0.0033	0.72	0.005		Yes

Effects on the development of the hypopharyngeal glands (HPGs):

Endpoint	SV	ETR	Trigger	Risk acceptable?
10d NOEL _{hpg} = 311.6 µg ai/bee/d	7.6 (down-ward application)	0.024	ETR > 1	Yes

Risk to honey-bee brood:

Test substance	Exposure route	Results	Risk acceptable?
Ethofol 500 SC	Honeybee brood feeding	No adverse effects on mortality, bee brood development (eggs, young larvae, old larvae, pupae) and colony development by feeding honey bee colonies sugar syrup at a concentration of 1.16 kg prod./ha, equivalent to 500 g ai/ha.	Yes

2.9.9.5. Risk assessment for non-target arthropods

Ethofumesate 500 SC

Test species	Application rate [g ai/ha]	MAF	Drift [%]	LR ₅₀ [g ai/ha]	HQ _{in-field}	HQ _{off-field}
<i>Aphidius rhopalosiphi</i>	1000	1	2.77	> 1000	< 1	< 0.03
<i>Typhlodromus pyri</i>		1		> 1000	< 1	< 0.03

Ethofol 500 SC:

species	Application rate [mL prod./ha]	MAF	Drift [%]	LR ₅₀ [g ai/ha]	HQ _{in-field}	HQ _{off-field}
<i>Aphidius rhopalosiphi</i>	2000	1	2.77	> 1000	< 1	< 0.03
<i>Typhlodromus pyri</i>		1		> 1000	< 1	< 0.03

2.9.9.6. Risk assessment for earthworms and other soil meso- and macro-organisms

Ethofumesate 500 SC:

GAP use	Test substance	NOEC [mg/kg soil dw]	max PEC _{soil} [mg/kg soil dw]	TER _{LT}	Risk acceptable?
Earthworms					
Sugar beets, red beet and fodder beets (post-emergence) 1 x 1 kg ai/ha	Ethofumesate 500 SC	NOAEC = 12.5 ai	1.069	11.7	Yes
	Metabolite NC 8493	NOEC = 16.0	0.233	68.7	Yes
<i>Folsomia candida</i>					
Sugar beets, red beet and fodder beets (post-emergence) 1 x 1 kg ai/ha	Ethofumesate 500 SC	NOEC = 22.05 ai	1.069	20.6	Yes
	Metabolite NC 8493	NOEC = 100	0.233	429	Yes
<i>Hypoaspis aculeifer</i>					
Sugar beets, red beet and fodder beets (post-emergence) 1 x 1 kg ai/ha	Ethofumesate 500 SC	NOEC = 220.5 ai	1.069	206	Yes
	Metabolite NC 8493	NOEC = 309	0.233	1326	Yes

Ethofol 500 SC:

GAP use	Test substance	NOEC [mg/kg soil dw]	max PEC _{soil} [mg/kg soil dw]	TER _{LT}	Risk acceptable?
Earthworms					
Sugar beets, fodder beets (pre-emergence) 1 x 1 kg ai/ha	Ethofol 500 SC	NOAEC = 5.25 ai	1.336	3.9	No
	Metabolite NC 8493	NOEC = 16.0	0.291	55	Yes
Sugar beets, fodder beets (post-emergence) 3 x 0.333 kg ai/ha	Ethofol 500 SC	NOAEC = 5.25 ai	0.357	15	Yes
<i>Folsomia candida</i>					
Sugar beets, fodder beets (pre-emergence) 1 x 1 kg ai/ha	Ethofol 500 SC	NOEC = 13.35 ai	1.336	10	Yes
	Metabolite NC 8493	NOEC = 100	0.291	344	Yes
<i>Hypoaspis aculeifer</i>					
Sugar beets, fodder beets (pre-emergence) 1 x 1 kg ai/ha	Ethofumesate 500 SC	NOEC = 22.1 ai	1.336	17	Yes
	Metabolite NC 8493	NOEC = 309	0.291	1062	Yes

2.9.9.7. Risk assessment for soil micro-organisms

Ethofumesate 500 SC:

Test substance	Effects < 25% at test concentration	PEC _{soil, accumulation}	Risk acceptable?
Ethofumesate 500 SC	13.0 mg ai/kg soil dw	1.069 mg ai/kg soil dw	Yes
Metabolite 8493	12.0 mg/kg soil dw	0.233 mg/kg soil dw	Yes

Ethofol 500 SC:

Test substance	Effects < 25% at test concentration	PEC _{soil, accumulation}	Risk acceptable?
Ethofol 500 SC	6.47 mg ai/kg soil dw	1.336 mg ai/kg soil dw	Yes
Metabolite 8493	12.0 mg/kg soil dw	0.291 mg/kg soil dw	Yes

2.9.9.8. Risk assessment for non-target plants

Ethofumesate 500 SC, 1 x 1000 gai/ha

Distance	Drift rate	Drift reducing nozzles	PER _{off-field} [L prod./ha]	Toxicity [L prod./ha]	TER	Risk acceptable ?
1 m	2.77%	-	0.0554	ER ₅₀ = 0.101	1.82	No
		50%	0.0277		3.65	No
		75%	0.01385		7.30	Yes
		90%	0.00554		18.25	Yes
5 m	0.57%	-	0.0114		8.87	Yes

Distance	Drift rate	Drift reducing nozzles	PER _{off-field} [L prod./ha]	Toxicity [L prod./ha]	TER	Risk acceptable ?
1 m	2.77%	-	0.0554	HC ₅ = 0.1882	3.40	Yes
		50%	0.0277		6.79	Yes
		75%	0.01385		13.59	Yes
		90%	0.00554		33.97	Yes
5 m	0.57%	-	0.0114		16.51	Yes

Ethofol 500 SC, 1 x 1000 g ai/ha

Distance	Drift rate	Drift reducing nozzles	PER _{off-field} [L prod./ha]	Toxicity [L prod./ha]	TER	Risk acceptable ?
1 m	2.77%	-	0.0554	ER ₅₀ = 0.328	5.92	Yes
		50%	0.0277		11.84	Yes
		75%	0.01385		23.68	Yes
		90%	0.00554		59.21	Yes
5 m	0.57%	-	0.0114		28.77	Yes

2.10. CLASSIFICATION AND LABELLING

Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification ¹⁾	Reason for no classification ²⁾
2.1.	Explosives	-	-	-	Conclusive, but not sufficient for classification
2.2.	Flammable gases	-	-	-	Conclusive, but not sufficient for classification
2.3.	Flammable aerosols	-	-	-	Conclusive, but not sufficient for classification
2.4.	Oxidising gases	-	-	-	Conclusive, but not sufficient for classification
2.5.	Gases under pressure	-	-	-	Conclusive, but not sufficient for classification
2.6.	Flammable liquids	-	-	-	Conclusive, but not sufficient for classification
2.7.	Flammable solids	-	-	-	Conclusive, but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-	-	-	Conclusive, but not sufficient for classification
2.9.	Pyrophoric liquids	-	-	-	Conclusive, but not sufficient for classification
2.10.	Pyrophoric solids	-	-	-	Conclusive, but not sufficient for classification
2.11.	Self-heating substances and mixtures	-	-	-	Conclusive, but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	Conclusive, but not sufficient for classification
2.13.	Oxidising liquids	-	-	-	Conclusive, but not sufficient for classification
2.14.	Oxidising solids	-	-	-	Conclusive, but not sufficient for classification
2.15.	Organic peroxides	-	-	-	Conclusive, but not

					sufficient for classification
2.16.	Substance and mixtures corrosive to metals	-	-	-	Conclusive, but not sufficient for classification
3.1.	Acute toxicity - oral	-	-	-	Conclusive, but not sufficient for classification
	Acute toxicity - dermal	-	-	-	Conclusive, but not sufficient for classification
	Acute toxicity - inhalation	-	-	-	Conclusive, but not sufficient for classification
3.2.	Skin corrosion / irritation	-	-	-	Conclusive, but not sufficient for classification
3.3.	Serious eye damage / eye irritation	-	-	-	Conclusive, but not sufficient for classification
3.4.	Respiratory sensitisation	-	-	-	Conclusive, but not sufficient for classification
3.4.	Skin sensitisation	-	-	-	Conclusive, but not sufficient for classification
3.5.	Germ cell mutagenicity	-	-	-	Conclusive, but not sufficient for classification
3.6.	Carcinogenicity	-	-	-	Conclusive, but not sufficient for classification
3.7.	Reproductive toxicity	-	-	-	Conclusive, but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	-	-	-	Conclusive, but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	Conclusive, but not sufficient for classification
3.10.	Aspiration hazard	-	-	-	Conclusive, but not sufficient for classification
4.1.	Hazardous to the aquatic environment	H400 H410	M = 1 M = 1	H411	-
5.1.	Hazardous to the ozone layer	-	-	-	Conclusive, but not sufficient for classification

¹⁾ Including specific concentration limits (SCLs) and M-factors

²⁾ Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Warning!
Hazard statements: H400 (M = 1), H410 (M = 1)
Precautionary statements: P273, P 391, P501,

Proposed notes assigned to an entry:

Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Justification:

H400/H410: Based on the study with the aquatic macrophyte *Myriophyllum spicatum* (Banman, C.S., 2011) with the active substance an endpoint for acute and chronic classification was derived. Based on the results on shoot length an E_rC_{50} of 0.479 mg a.i./L and a NOE_rC of 0.036 mg a.i./L was determined.

Under consideration of the not rapid degradability of the active substance ethofumesate in the water sediment system the active substance has to be classified as aquatic hazardous, acute and chronic cat. 1.

2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

In the environmental fate and behaviour section of this renewal assessment it was concluded that in soil degradation studies no metabolites were identified as requiring 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*.

In the soil photolysis study (Stupp and Weuthen, 2013), metabolite NC 8493 (ethofumesate-2-hydroxy) was identified > 5% AR.

The 80th percentile annual average PEC_{gw} concentrations at 1m depth were predicted as <0.001 µg/l for NC-8493 in all cases.

STEP 1: Exclusion of degradation products of no concern

According to *Guidance document on the assessment of the relevance of the metabolites in groundwater of substances regulated under Council Directive 91/414/EEC (Sanco/221/2000 –rev.10- final, 25 February 2003)* no degradation products of concern were detected.

2.11.1. STEP 2: Quantification of potential groundwater contamination

The leaching simulations resulted in PEC_{GW} values below 0.1 µg L⁻¹ for ethofumesate and its metabolites NC20645 and NC8493 for all intended uses and all relevant FOCUS scenarios using FOCUS PEARL 4.4.4. The risk for groundwater leaching is considered low.

2.11.2. STEP 3: Hazard assessment – identification of relevant metabolites

STEP 3, Stage 1: screening for biological activity

Not necessary since no metabolite predicted > 0.1 µg/l in groundwater. The TaskForce Ethofumesate submitted a study on biological activity of metabolite NC 20645, for details please see Volume 3 CA B3.

STEP 3, Stage 2: screening for genotoxicity

Not necessary since no metabolite predicted > 0.1 µg/l in groundwater. The TaskForce Ethofumesate submitted *in vitro* battery of genotoxicity studies with sodium salt of metabolite NC 20645, for details please see Volume 3 CA B6.

STEP 3, Stage 3: screening for toxicity

Not necessary since no metabolite predicted > 0.1 µg/l in groundwater.

2.11.3. STEP 4: Exposure assessment – threshold of concern approach

Not necessary since no metabolite predicted > 0.1 µg/l in groundwater.

2.11.4. STEP 5: Refined risk assessment

Not necessary since no metabolite predicted > 0.1 µg/l in groundwater.

2.11.5. Overall conclusion

Not necessary since no metabolite predicted > 0.1 µg/l in groundwater.

2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.12.1. Identity and physical chemical properties

Since Ethofumesate is a racemic mixture and stable with the constant proportion of isomers (R:S 50:50) no testing of physical-chemical properties of the individual enantiomers is required.

2.12.2. Methods of analysis

Since Ethofumesate is a racemic mixture and stable with the constant proportion of isomers (R:S 50:50) no enantiomer selective analytical methods are required.

2.12.3. Mammalian toxicity

All toxicological studies were performed with racemic material ((*R/S*)-Ethofumesate). As Ethofumesate racemic material is stable with the constant proportion of isomers (50:50), no further data on possible stereoselective toxicity is required.

2.12.4. Operator, Worker, Bystander and Resident exposure

All toxicological studies were performed with racemic material ((*R/S*)-Ethofumesate). As Ethofumesate racemic material is stable with the constant proportion of isomers (50:50), no further data on possible stereoselective toxicity is required.

2.12.5. Residues and Consumer risk assessment

All studies were performed with racemic material ((*R/S*)-Ethofumesate). As Ethofumesate racemic material is stable with the constant proportion of isomers (50:50), no further data on possible stereoselective toxicity is required.

2.12.6. Environmental fate

All environmental fate studies were performed with racemic material ((*R/S*)-Ethofumesate). As Ethofumesate racemic material is stable with the constant proportion of isomers (50:50), no further data on possible stereoselective toxicity is required.

2.12.7. Ecotoxicology

All ecotoxicological studies were performed with racemic material ((*R/S*)-Ethofumesate). As Ethofumesate racemic material is stable with the constant proportion of isomers (50:50), no further data on possible stereoselective toxicity is required.

2.13. RESIDUE DEFINITIONS

2.13.1. Definition of residues for exposure/risk assessment

Food of plant origin: Ethofumesate, 2-keto-ethofumesate (NC 9607), open-ring-2-keto-ethofumesate (NC 20645) and its conjugate

Food of animal origin: Ethofumesate, 2-keto-ethofumesate (NC 9607), open-ring-2-keto-ethofumesate (NC 20645)

Soil: ethofumesate, NC 8493 (ethofumesate-2-hydroxy)

Groundwater: ethofumesate, NC 8493(ethofumesate-2-hydroxy), NC 20645 (ethofumesate-carboxylic acid)

Surface water: ethofumesate, NC 8493(ethofumesate-2-hydroxy), NC 20645 (ethofumesate-carboxylic acid),BCS-CW35117 (ethofumesate-acetic acid)

Sediment: ethofumesate, NC 20645 (ethofumesate-carboxylic acid)

Air: ethofumesate

2.13.2. Definition of residues for monitoring

Food of plant origin: Ethofumesate, 2-keto-ethofumesate (NC 9607), open-ring-2-keto-ethofumesate (NC 20645) and its conjugate

Food of animal origin: Ethofumesate, 2-keto-ethofumesate (NC 9607), open-ring-2-keto-ethofumesate (NC 20645)

Soil: ethofumesate

Groundwater: ethofumesate

Surface water: ethofumesate

Sediment: ethofumesate

Air: ethofumesate

Level 3

ETHOFUMESATE

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 Ethofumesate for the representative uses (please refer to Section 1.5.1 Level 1 for details of representative uses)			
3.1.1.2. Submission of further information			
		Yes	No
i)	It is considered that a complete dossier has been submitted	X	
With regards to the submission made, a complete dossier is considered to have been submitted, which enables a regulatory decision of Ethofumesate to be made. Regarding the data gaps identified in the separate dossiers of the notifiers please refer to point 3.1.4.			
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.		
Not applicable			
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; The minimum purity should be specified as 960 g/kg (reference source DAR 1998). This is unchanged from the purity specified in the current approval and is supported by the most recent batch analysis from all			

				<p>notifiers.</p> <p>(b) <i>the nature and maximum content of certain impurities;</i> No relevant impurities were specified in the past and are not supported by the current five batch analysis of the notifiers. However, (according to the FAO specification for ethofumesate (233/TC (January 2007)) ethyl methane sulfonate and/or iso-butyl methane sulfonate can occur as a result of certain manufacturing processes. If these impurities occurred at ≥ 0.1 mg/kg (relative to ethofumesate) in the products of other manufacturers, they would be designated as relevant impurities and clauses would be required to limit their concentration.</p> <p>(c) <i>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;</i> N/A</p> <p>(d) <i>type of preparation;</i> N/A</p> <p>(e) <i>manner and conditions of application;</i> The maximum amount of active substance per season per hectare must not exceed 1.0 kg. every 3 years</p> <p>(f) <i>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;</i> N/A</p> <p>(g) <i>designation of categories of users, such as professional and non-professional;</i> N/A</p>
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				<p>(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;</p> <p>N/A</p> <p>(i) the need to impose risk mitigation measures and monitoring after use</p> <p>Risk mitigation measures (e.g. vegetated buffer strip) are required to address the risk to aquatic organisms.</p> <p>(j) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009.</p> <p>N/A</p>
3.1.1.4. 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) and Acceptable Operator Exposure Level (AOEL). Results from the toxicological studies do not raise the need for setting an Acute Reference Dose (ARfD).
	<p>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:</p> <p>(a) permits any residue of concern to be defined;</p> <p>(b) reliably predicts the residues in food and feed, including succeeding crops</p> <p>(c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing;</p> <p>(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;</p>			<p>The data necessary to establish adequate MRLs and consumer risk assessment were submitted are considered as sufficient for the current approval process.</p> <p>Based on the assessment of the available data, MRL proposals were derived and a consumer risk assessment was carried out. No risk for consumers could be identified with respect to the representative uses.</p>

	(e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			
	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		See detailed evaluation in sections 8 and 9.
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		Sufficient information on efficacy of ethofumesate was provided by all notifiers. For details please see Level 2, Section 2.3
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		The toxicological, ecotoxicological or environmental relevance of metabolites can be established.
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/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		Sufficient information has been presented by all notifiers to support the declared technical specification of ethofumesate with respect to the identity and content of impurities in the respective technical specifications.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	X		The technical specifications provided independently by the notifiers comply with the minimum purity level of 960 g/kg, as stated in the FAO specification for ethofumesate (233/TC (January 2007)). Further in the FAO specification is stated that <i>ethyl methane sulfonate and/or iso-butyl methane sulfonate can occur as a result of certain manufacturing processes. If these impurities could occur at ≥ 0.1 mg/kg (relative to ethofumesate) in the products of other manufacturers, they would be designated as relevant impurities and clauses would be required to limit their concentration.</i>
	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			Not necessary
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance,	X		Adequate analytical methods are available for the determination of

	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.			ethofumesate and all significant impurities in the technical material. Analytical methodology is available for the technical compound as well as for the formulated product if ethyl methane sulfonate and iso-butyl methane sulfonate are considered to be relevant.
	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		Adequate methods are available and sufficiently sensitive to monitor the respective current residue definition in plant material, soil, drinking water, surface water and air.
	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		Please refer to Level 2 Section 2.2 for further details The information submitted with regards to methods of analysis is sufficient to support approval. Refer also to Level 2, Section 2.5.
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 1 mg/kg bw/d is proposed based on the application of a standard safety factor of 100 to the NOAEL of 101 mg/kg bw/d, identified for females in the rat 2-yr chronic toxicity and carcinogenicity study. Results from the toxicological studies do not raise the need for setting an Acute Reference Dose (ARfD). The AOEL of 2.5 mg/kg bw/d is proposed based on the application of the standard safety factor of 100 to the NOAEL of 250 mg/kg bw/d identified in 90 days dog study. No correction factor for oral absorption is considered necessary.
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	Ethofumesate was tested negative in the standard range of <i>in vitro</i> and <i>in vivo</i> genotoxicity tests. Classification for mutagenicity is not warranted. Please also refer to Level 2, Section 2.6.4.

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 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 .		X	No treatment related neoplastic findings were observed in any of the studies Ethofumesate is not carcinogenic, neither in rats nor in mice. Classification for carcinogenicity is not warranted.
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.			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 ethofumesate has been adequately investigated in rat multigeneration studies and in rat and rabbit developmental toxicity studies. These studies demonstrated that ethofumesate does not possess hazardous properties in relation to fertility, reproductive performance or development. Classification for reproductive toxicity is not warranted.
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.			Not applicable
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	No evidence of carcinogenicity or reproductive toxicity was seen in the standard carcinogenicity and reproductive toxicity studies.
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 reproductive toxicity was seen in the standard carcinogenicity and reproductive toxicity studies. No evidence of toxic effects on endocrine organs was seen throughout the whole ethofumesate dossier.
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.			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	Persistence: The DT50 in water is above the trigger of 2 months (331-1000 d in aerobic surface water mineralization study). Bioaccumulation: The bioconcentration factor ($BCF_{fish} = 144$) and the partition co-efficient ($\log P_{OW} = 2.7$) are below the trigger of 5000 and > 5 , respectively. No indication for long range transport
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	Persistence: DT50 in fresh water is above the trigger of 40 d (331-1000 d in aerobic surface water mineralization study); the DT50 in sediment is above the trigger of 120 d (geomean in sediment 281 d) Bioaccumulation: The bioconcentration factor ($BCF_{fish} = 144$) is below the trigger of 2000.

				<p>Toxicity: The NOEC values for marine and freshwater species are above the trigger of > 0.01 mg ai/L.</p> <p>Ethofumesate is not classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) or STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008</p>
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance FULFILS the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	<p>Persistence: The DT50 in fresh water is above the trigger of 40 d (331-1000 d in aerobic surface water mineralization study); the DT50 in sediment is above the trigger of 120 d (geomean in sediment 281 d)</p> <p>Bioaccumulation: The bioconcentration factor is below the trigger of 5000 ($BCF_{fish} = 144$).</p>
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		<p>The intended use is a spray application (pre- and post-emergence) on sugar beets, fodder beets and red beets.</p> <p>Based on the available studies no adverse effects on non-target organisms were identified.</p> <p>However, the long-term risk to earthworms from exposure to the EU representative formulation Ethofol 500 SC could not be finalised ($TER_{LT} = 3.9$) considering the pre-emergence application of 1 x 1000 g ai/ha.</p> <p>For further information please refer to Level, Section 2.9.</p>
	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	<p>There are currently no defined criteria for identifying endocrine disruptors under Regulation (EC) 1107/2009.</p> <p>From the toxicological point of view no evidence of carcinogenicity or reproductive toxicity was seen in the reproductive toxicity studies. No evidence of adverse effects on endocrine organs was observed. There is currently no concern regarding endocrine disruption.</p>
	<p>Linked to the consideration of the endocrine properties immediately above.</p> <p>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.</p>		X	<p>An exposure of non-target organisms based on the proposed GAP uses cannot be excluded.</p> <p>There are currently no defined criteria for identifying endocrine disruptors under Regulation (EC) 1107/2009.</p> <p>However, from the toxicological point of view no evidence of carcinogenicity or reproductive toxicity was seen in the reproductive toxicity studies. No evidence of adverse effects on endocrine organs was observed. There is currently no concern regarding endocrine disruption.</p>

	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 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.	X		Laboratory studies on acute oral and contact toxicity and on chronic toxicity to adult honey-bees were conducted by both notifiers. In addition, studies on honey-bee brood were submitted. Based on the available data and the outcome of the risk assessment considering all GAP uses (pre- and post-emergence) no risks to honey-bees considering adult and larvae mortality, effects on honey-bee populations and chronic effects were identified. For a detail summary please refer to Level 2, Section 2.9.
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.			The data were sufficient to propose the following residue definition for enforcement: Plants: Ethofumesate, 2-keto-ethofumesate (NC 9607), open-ring-2-keto-ethofumesate (NC 20645) and its conjugate Animals: Ethofumesate, 2-keto-ethofumesate (NC 9607), open-ring-2-keto-ethofumesate (NC 20645)
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 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.	X		Ethofumesate or its metabolites are not predicted to occur in groundwater above 0.1 µg/L.

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	<p>Ethofumesate does not meet the criteria to be considered as a candidate for substitution (as bellow):</p> <ul style="list-style-type: none"> - <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> - NO — <i>it meets two of the criteria to be considered as a PBT substance</i> –NO — <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> – NO — <i>it contains a significant proportion of non-active isomers</i> – NO — <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> - NO — <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-</i> NO — <i>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.]-</i> NO
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3.1.3. Proposal – Low risk active substance

Low-risk active substances			
	Yes	No	
<p>It is considered that the active substance shall be considered of low risk.</p> <p>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:</p> <ul style="list-style-type: none"> — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. <p>In addition it is considered that the substance is NOT:</p> <ul style="list-style-type: none"> — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disruptor, or — has neurotoxic or immunotoxic effects. 		X	<p>Ethofumesate cannot be considered a low risk substance because it should be classified in accordance with Regulation (EC) No 1272/2008 as “Very toxic to aquatic life with long lasting effects” (H400; H410)</p> <ul style="list-style-type: none"> - classified or to be classified as carcinogenic – NO - classified or to be classified as mutagenic – NO - classified or to be classified as toxic to reproduction – NO - classified or to be classified as sensitising – NO - classified or to be classified as very toxic or toxic – YES (H400; H410) - classified or to be classified as explosive – NO - classified or to be classified as corrosive – NO <ul style="list-style-type: none"> - persistent – NO (90th percentile lab studies: 27.5 d) - bioconcentration factor higher than 100 – YES - endocrine disruptor – NO (based on current knowledge) - neurotoxic or immunotoxic effects - NO

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				
None				
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				
None				

3.1.4.6. Toxicology and metabolism				
None				
3.1.4.7. Residue data				
None				
3.1.4.8. Environmental fate and behaviour				
<p>United Phosphorous Ltd.:</p> <p>Soil photolysis metabolite NC8493 occurred at > 10% AR. The groundwater exposure assessment for soil photolysis metabolite NC 8493 could not be finalised, since its adsorption onto soil was not investigated. Adsorption/desorption studies on NC8493 in soil and the respective PECGW calculations shall be submitted by the notifier.</p>	Pre-emergence and post-emergence application on sugar- and fodder beets	No information that studies are available or on-going.		
<p>United Phosphorous Ltd.:</p> <p>Metabolites NC20645 was found to be responsible for the previously detected and not further characterized "Peak A" occurring in a lysimeter study. It was found that groundwater exposure assessment was necessary. The groundwater exposure assessment for soil/lysimeter metabolite NC 20645 could not be finalised. Adsorption and degradation studies on NC20645 and the respective PECGW calculations shall be submitted.</p>	Pre-emergence and post-emergence application on sugar- and fodder beets	No information that studies are available or on-going.		
<p>United Phosphorous Ltd.:</p> <p>The submitted soil photolysis study was regarded as not valid. A valid soil photolysis study shall be</p>	Pre-emergence and post-emergence application on sugar- and fodder beets	No information that studies are available or on-going.		

submitted.				
<p>United Phosphorous Ltd.:</p> <p>The metabolite CW 35117, which occurs > 10% in an aerobic surface water mineralization study needs to be characterized. The exposure assessment for surface water and sediment could not be finalized. Therefore, an aerobic degradation study and adsorption/desorption behaviour shall be submitted by the notifier.</p>	Pre-emergence and post-emergence application on sugar- and fodder beets	No information that studies are available or on-going.		
3.1.4.9. Ecotoxicology				
<p>United Phosphorous Ltd.:</p> <p>The risk assessment for earthworms regarding the active substance/representative formulation could not be finalised based on the available data. Further data are required to address the risk for earthworms.</p>	Pre-emergence application on sugar- and fodder beets	No information that studies are available or on-going.	-	-
<p>United Phosphorous Ltd.:</p> <p>The risk assessment for aquatic organisms from exposure to the metabolite ethofumesate acetic acid could not be finalised based on the available data.</p> <p>The metabolite was identified in water sediment study conducted by the notifier Task Force Ethofumesate. In the water sediment study conducted by UPL this metabolite could not be identified.</p> <p>During the assessment of the active substance the metabolite ethofumesate acetic acid was considered relevant for the ecotoxicological risk assessment. Hence, further data are required addressing the risk to aquatic organisms from exposure to the metabolite</p>	Pre- and post-emergence application on sugar- and fodder beets	No information that studies are available or on-going.	-	-

<p>United Phosphorous Ltd.:</p> <p>The risk assessment for algae could not be finalised based on the available studies with algae.</p> <p>The active substance ethofumesate is an herbicide; hence, at least two species of algae of different taxonomic groups have to be tested. However, only studies with green algae are available to address the risk. At least one additional study with different species of algae has to be tested to address the data requirements.</p>	<p>Pre- and post-emergence application on sugar- and fodder beets</p>	<p>No information that studies are available or on-going.</p>	<p>-</p>	<p>-</p>
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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)
1. The risk assessment for the active substance ethofumesate could not be finalised considering the risk to algae (United Phosphorous Ltd., all uses).	Pre- and post-emergence application on sugar and fodder beets (representative formulation Ethofol 500 SC)
2. The risk assessment for aquatic organisms from exposure to the metabolite ethofumesate acetic acid could not be finalised (United Phosphorous Ltd., all uses).	Pre- and post-emergence application on sugar and fodder beets (representative formulation Ethofol 500 SC)
3. The risk assessment for the active substance ethofumesate could not be finalised considering the long-term risk to earthworms (United Phosphorous Ltd., pre-emergence application)	Pre-emergence application on sugar and fodder beets (representative formulation Ethofol 500 SC)
4. The groundwater exposure assessment for soil photolysis metabolite NC 8493 could not be finalised (United Phosphorous Ltd., pre- and post-emergence application).	Pre- and post-emergence application on sugar and fodder beets (representative formulation Ethofol 500 SC)
5. The groundwater exposure assessment for soil/lysimeter metabolite NC 20645 could not be finalised (United Phosphorous Ltd., pre- and post-emergence application).	Pre- and post-emergence application on sugar and fodder beets (representative formulation Ethofol 500 SC)
6. The risk assessment regarding soil photolysis could not be finalized (United Phosphorous Ltd., pre- and post-emergence application).	Pre- and post-emergence application on sugar and fodder beets (representative formulation Ethofol 500 SC)
7. The exposure assessment for surface water and sediment regarding metabolite CW 35117 could not be finalized (United Phosphorous Ltd., pre- and post-emergence application).	Pre- and post-emergence application on sugar and fodder beets (representative formulation Ethofol 500 SC)

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)
None identified in the renewal assessment	Not applicable

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)

Representative use		Beets (sugar-, fodder-, red beet) Pre-emergence	Beets (sugar-, fodder-, red beet) Post-emergence
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	X ³	-
Risk to aquatic organisms	Risk identified	-	-
	Assessment not finalised	X ^{1, 2}	X ^{1, 2}
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	X ^{4,5,6,7}	X ^{4,5,6,7}
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
None	-

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.

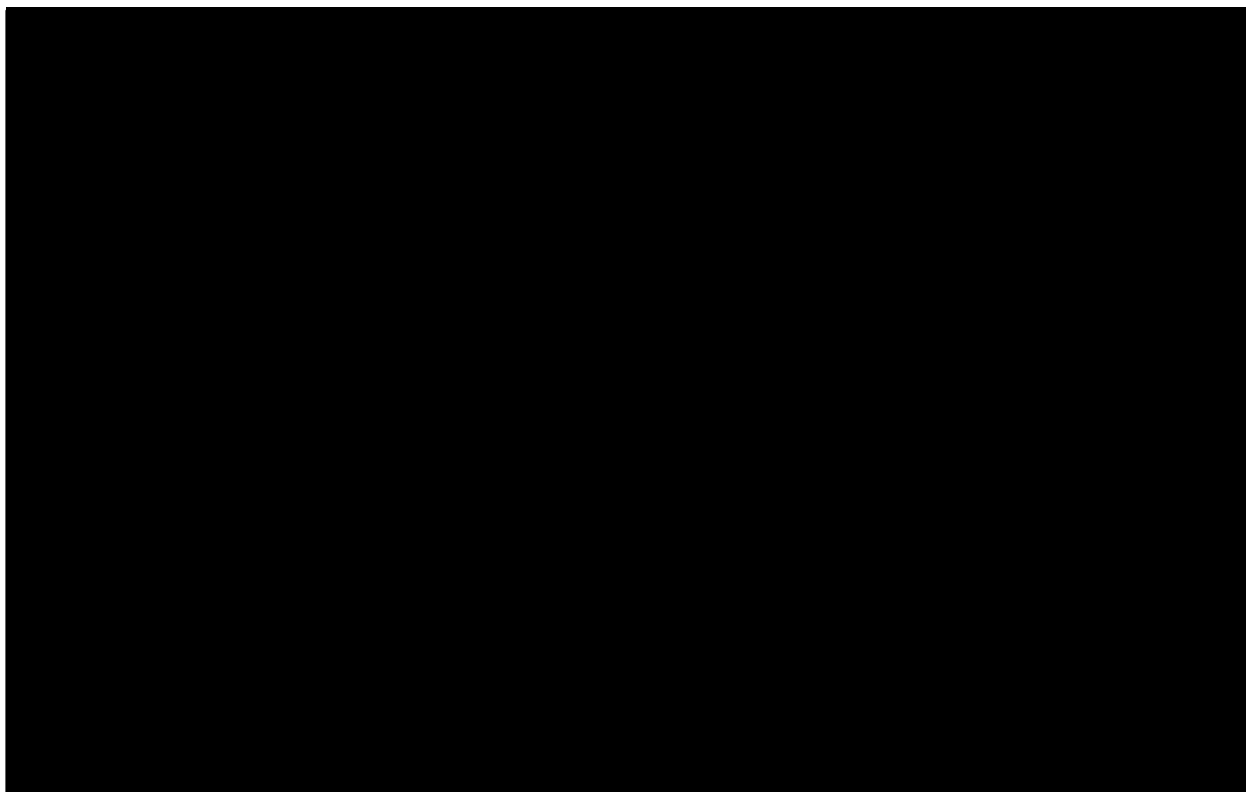
Issue on which Co-RMS disagrees with RMS	Opinion of Co-RMS	Opinion of RMS
Probabilistic risk assessment on non-target plants (Notifier: Task Force, Ethofumesate 500 SC)	The Co-RMS has some concerns on the use of the probabilistic approach. The Co-RMS is of the opinion that the proposed safety factor of 1 should not be applied as the most sensitive species (wheat, $ER_{50} = 0.101$ L prod./ha) is not covered by the HC_5 ($HC_5 = 0.1882$ L prod./ha).	The RMS agrees with the Co-RMS that the most sensitive species is not covered by the HC_5 value. However, the RMS is of the opinion that the use of the probabilistic approach is acceptable. Even under consideration of a higher safety factor (e.g. 3 instead of 5) an acceptable risk to non-target plants was identified. In addition, the use of risk mitigation measures (e.g. 50% drift reducing nozzles or 5 m buffer zones) is also considered in the dRAR.
Probabilistic risk assessment on non-target plants (Notifier: Task Force, Ethofumesate 500 SC)	The calculation of the HC_5 value is based on ER_{50} values derived from two seedling emergence studies. No “greater than” values were included in the risk assessment. The Co-RMS proposed to include “greater than” values based on the recommendations given in the newly noted aquatic guidance document (EFSA Journal 2013;11(7):3290). According to the recommendations in the new aquatic guidance document the greater- or lower than value should only be included (without the < or > sign) in the calculation of the SSD for that species if it is outside the range of already available values.	At the time of the assessment of ethofumesate the aquatic guidance document was not noted. Hence, the risk assessment was based on the current available guidance and information on the SSD approach.
Soil dissipation studies (Baseline dossier).	Co-RMS does not agree that the weather conditions in the North Dakota study are not representative	The RMS is of the opinion that the field study in North Dakota (with calculated soil temperatures below -20°C) is not representative for

	<p>for European sugar beet scenarios.</p> <p>The soil and air temperatures of the study report are not uncommon in northern Europe.</p> <p>Furthermore the latitude of North Dakota 45-49°N is representative for Europe.</p>	European sugar beet scenarios.
Use of 0.5 as plant uptake factor in PEC_{GW} and PEC_{SW} calculations.	The Co-RMS is of the opinion that the use of a plant uptake factor has been discussed at several expert meetings and that the prevailing opinion is that a plant uptake factor cannot be used unless studies on plant uptake are presented.	The RMS does not agree. Based on FOCUS (2000 and 2009), a default factor of 0 for non-systemic and a default factor of 0.5 for systemic substances has been used in the risk assessment.

3.2. PROPOSED DECISION

It is proposed that:





**3.3. RATIONAL 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)

3.4. APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

Volume 3 – B1: Identity

None

Volume 3 - B2: Physicochemical properties

None

Volume 3 - B5: Analytical methods

Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3029/99 rev. 4)

Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3030/99 rev. 4)

Guidance document on pesticide residue analytical methods (SANCO/825/00 rev. 8.1)

Volume 3 - B6: Toxicology and metabolism of the active substance

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092

EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665

Guidance on the Application of the CLP Criteria, Version 2.0 (April 2012)

Guidance document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) 283/2013 and Regulation (EU) No 284/2013 (SANCO/10181/2013– rev. 2, May 2013)

Guidance Document 8064/VI/97 rev. 4 on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated Under Council Directive 91/414/EEC (SANCO/221/2000 rev. 10 25 February 2003)

Volume 3 - B7: Residues

EC (European Commission), 2011. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs; 7525/VI/95-rev.9

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092

Guidance document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) 283/2013 and Regulation (EU) No 284/2013 (SANCO/10181/2013– rev. 2, May 2013)

OECD (Organisation for Economic Co-operation and Development), 2011; OECD MRL Calculator: User Guide. In: Series on Pesticides No 56. ENV/JM/MONO(2011)2, 01 March 2011.

Volume 3 - B8: Environmental Fate and Behaviour

FOCUS (2006) Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration. Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp

FOCUS (2009). Assessing Potential for Movement of Active Substances and their Metabolites to Ground Water in the EU. Report of the FOCUS Ground Water Work Group, EC Document Reference Sanco/13144/2010 version 1, 604 pp.

EFSA (2014). EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014; 12(5):3662, 37pp.

FOCUS (2007). Landscape And Mitigation Factors In Aquatic Risk Assessment. Volume 1. Extended Summary and Recommendations. Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment, EC Document Reference SANCO/10422/2005 v2.0. 169 pp.

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092.

Volume 3 - B9: Ecotoxicology

Guidance Document on Aquatic Ecotoxicology in the context of the Directive 91/414/EEC, SANCO/3268/2001 rev. 4 (final), 17 October 2002

Risk Assessment for Birds and Mammals, EFSA Journal 2009;7(12):1438

Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/141/EEC, SANCO/10329/2002, 17 October 2002 rev. 2 final

Candolfi et al., 2000, Guidance Document on Regulatory Testing and Risk Assessment Procedures for Plant Protection Products with Non-Target Arthropods, ESCORT 2 SETAC Workshop

EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus spp.* and solitary bees), EFSA Journal 2013;11(7):3295

EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092

Guidance document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) 283/2013 and Regulation (EU) No 284/2013 (SANCO/10181/2013– rev. 2, May 2013)

Volume 4 Annex C:

Guidance document on the assessment of the equivalence of technical materials of substances regulated under regulation (EC) No 1107/2009 (SANCO/10597/2003 –rev. 10)

3.5. REFERENCE LIST

No references specifically cited in Volume 1